EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER

THE BURDEN OF **LIVER DISEASE** IN EUROPE

A REVIEW OF AVAILABLE EPIDEMIOLOGICAL DATA

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OVERVIEW

The past 30 years have witnessed major progress in the knowledge and management of liver disease, yet approximately 29 million people in the European Union still suffer from a chronic liver condition. Difficulties in accessing data from individual countries hinder global evaluation of liver disease in Europe. This report reviews 260 epidemiological studies published in the last five years to survey the current state of evidence on the burden of liver disease in Europe and its causes.

The incidence and prevalence of two conditions, cirrhosis and primary liver cancer, are key to understanding the burden of liver disease. They represent the end-stage of liver pathology and thus are indicative of the associated mortality. Literature on the prevalence and incidence of cirrhosis is scarce. However, available data suggest that about 0.1% of the European population is affected by cirrhosis, corresponding to 14-26 new cases per 100,000 inhabitants per year or an estimated 170,000 deaths per year [2]. There are, however, large intra-European variations. About 0.1% of Hungarian males will die of cirrhosis every year compared with 0.001% of Greek females.

Hepatocellular carcinoma (constituting 70-90% of cases of primary liver cancer) is the fifth most common cause of cancer in Europe and one of the most serious outcomes of cirrhosis. European epidemiological data show that there are 1-13 new cases of hepatocellular carcinoma and 1-10 deaths per 100,000 inhabitants per year. WHO estimate that liver cancer is responsible for around 47,000 deaths per year in the EU.

The four leading causes of cirrhosis and primary liver cancer in Europe are harmful alcohol consumption, viral hepatitis B and C and metabolic syndromes related to overweight and obesity.

Chronic alcohol consumption is the main cause of cirrhosis in Europe. Alcohol consumption decreased in the 1990s, but has increased again in the last decade to stabilize at a high level of >9 litres of pure alcohol per year on average, although there are large variations among European countries.

Chronic viral hepatitis B is the second major cause of both cirrhosis and liver cancer. Between 0.5% and 0.7% of the European population is affected by chronic hepatitis B, with the highest prevalence being recorded in Romania (5.6%) and Greece (3.4%). By comparison, HIV prevalence is only 0.2% (HIV is 50-100 times less infectious). The availability of a vaccine has resulted in a decrease in the prevalence of HBV, although it remains responsible for 30% of cases of cirrhosis and 15% of cases of primary liver cancer.

Chronic hepatitis C is an important risk factor for hepatocellular carcinoma, which develops several decades after infection. Since the discovery of the virus in the late eighties, the number of new cases of infection has dropped substantially. Prevalence rates of hepatitis C virus (HCV) infection in the last decade in the European population were between 0.13 and 3.26%, the highest rates being found in Italy and Romania. These HCV-infected populations will develop complications in the years to come, leading to a substantial increase in the burden of disease. It is of great concern that about 90% of people in Europe infected by viral hepatitis are unaware of their status.

Non-alcoholic fatty liver disease (NAFLD) is becoming a major concern with the increasing incidence of obesity in Europe. In this condition, accumulation of fat in the liver leads to chronic liver disease. Available data suggest the prevalence rate of NAFLD is 2–44% in the general European population (including obese children) and 42.6–69.5% in people with type 2 diabetes. NAFLD increases the risk of cirrhosis and liver cancer.

Each of these four major causes of liver disease is amenable to prevention and treatment, reducing the burden of liver disease in Europe and saving lives. However, epidemiological data are scarce. Additional surveys are urgently needed to provide reliable information, without which it will not be possible to implement cost-effective prevention programmes and novel treatments to tackle liver disease and avoidable deaths in Europe.

INTRODUCTION

The past 30 years have witnessed major progress in the knowledge and management of liver disease yet approximately 29 million persons in the European Union still suffer from a chronic liver condition. Difficulties in accessing data from individual countries hinder comprehensive evaluation of the burden of liver disease in Europe and comparison with other diseases. Moreover, very few reviews have studied both chronic liver conditions, such as cirrhosis and cancer, and their major causes, such as viral hepatitis, alcohol intake and metabolic syndrome. It is likely that the causes of chronic liver diseases differ from country to country but no reliable data exist about this. A large systematic review of all epidemiological data available for European countries has hitherto not been undertaken.

Here we review evidence of the burden and causes of liver disease in Europe, drawing on a survey of all epidemiological data published over the course of the last five years.

METHODS

MEDLINE, EMBASE, and the Cochrane Library were searched for relevant articles using the following medical subject headings (MeSH) terms 'liver' and ['disease' or 'epidemiology']. The search encompassed articles published throughout the last five years in any European language. Studies were included if: (1) they presented epidemiological data; (2) they included patients who lived in the European Union (EU27) or Norway (but not necessarily exclusively so); (3) they were published or accepted for publication as full-length articles. Studies were excluded if: (1) they estimated prevalence or incidence from data collected before 1995; (2) they studied very specific populations; (3) they were published only in abstract form so that the methodological quality could not be assessed. When the results of a single study were reported in more than one publication, only the most recent and complete data were included in the systematic review.

A manual search of references cited in retrieved articles was also conducted to identify studies not found in the database search. Data presented in World Health Organization (WHO) reports, in European Centre for Disease Prevention and Control (ECDC) reports and on EUROHEP.NET were also included.

All available data on liver disease incidence and prevalence and on associated mortality and trends were extracted from the reviewed articles. Most mortality statistics were derived from official causes of death recorded on death certificates. Of 4,256 reviewed studies, 260 met the inclusion criteria.

The European Liver Transplant Registry (ELTR) was used to describe the epidemiology of liver transplantation in Europe as it represents more than 95% of all official published European data (Fig. 5, page 16).

Geographical factors necessitate caution in the interpretation of parts of this review for two reasons: (1) inter-country variation in death-reporting processes; therefore caution must be exercised when making comparisons between countries; (2) the definition of the European zone varies according to the source, so care must be taken when assessing data reported at the European level. According to WHO, European countries include all eastern and central European countries as well as the Russian Federation. By contrast, data given for the EU27 refer only to countries that belong to the European Union.

RESULTS

CIRRHOSIS

According to WHO, liver cirrhosis accounted for 1.8% of all deaths in Europe (using WHO's wide geographical definition), causing around 170,000 deaths per year. In the last decades of the 20th century, a very strong east-west gradient in mortality rates was observed, with the level of liver cirrhosis mortality in south-eastern Europe (especially in Hungary and Moldova but also in Slovakia, Slovenia and Romania) and in north-eastern European countries achieving rates never before seen in Europe [1, 2] (figs. 1 and 2, see page 9 and 11). However, in recent years, liver cirrhosis has also become a serious health threat in some Western European countries, such as the United Kingdom and Ireland, where over the last 10 years the associated mortality has increased.

Alcohol has long been identified as the strongest risk factor for liver cirrhosis [3, 4]. In fact, cirrhosis mortality has traditionally been used as a valid indicator for tracing the health consequences of alcohol abuse. However, infections by the hepatitis B and C viruses (HBV and HCV) are also important determinants of cirrhosis, and their possible contribution to temporal trends should be taken into account. Zatonski et al. studied the temporal trends of liver cirrhosis in European countries, based on the WHO mortality database (http://data.euro.who.int) [2]. Radical increases in liver cirrhosis mortalities were observed from the 1970's within a group of several South-Eastern European countries. Hungary was an especially dramatic example. From the mid-1970's to the mid-1990's, cirrhosis mortality rates in Hungary increased from 20 to 148 per 100,000 males (the highest level ever registered in any European country) and from about 8 to 48 per 100,000 females [2]. By 2002 these rates had slightly declined to 103 per 100,000 males and 32 per 100,000 females [2]. Another group of countries in which dramatic changes were observed were the North-Eastern European countries (former Soviet Union countries such as Estonia, Latvia, Lithuania and Poland). For the reasons already stated, it is difficult to compare mortality rates from one country to another, but the trends are unmistakable. In contrast, in the Mediterranean region (France, Italy, Spain, Portugal and Greece) appreciable declines in cirrhosis mortality were observed in populations that historically had the highest cirrhosis mortality levels in both sexes. HBV vaccine, reduced alcohol consumption and reduction of HCV transmission have probably contributed to this decrease. A recent French study might appear to buck this trend, finding 0.3% of screened males aged more than 40 years old to have liver cirrhosis [5]. However, these results should be interpreted with caution as the subjects were seen within a free screening programme and therefore were potentially at high risk of liver fibrosis [5]. The associated causes of liver disease in this study were a combination of alcoholic and NAFLD (66%), NAFLD only (13%), alcohol (9%), HCV (6%), and other causal factors (6%) [5]. Factors independently associated with fibrosis were age, male gender, waist circumference, presence of HCV antibody and alcohol consumption [5]. These results suggest that alcohol and NAFLD are two causal factors with the potential to keep levels of liver cirrhosis relatively high in western European countries.

Among north European countries, there was about a two-fold increase in cirrhosis rates in the UK and Ireland until the 1990s, according to the WHO mortality database [2]. This is confirmed by a study based on the UK General Practice Research Database (GPRD), where the prevalence of liver cirrhosis increased by almost 50% between 1992 and 2001 to 76.3 per 100,000 persons (Table 1, page 10) [6]. In another UK study, the incidence rate of cirrhosis was 26 per 100,000 women between 1996 and 2005 [7]. In a nationwide, population-based registry study in Denmark, liver cirrhosis

prevalence remained high between 1996 and 2005 [8]. In 2005, the alcoholic cirrhosis incidence rates were 26.5 (25.7-17.4) and 11.8 (11.2-12.4) per 100,000 per year for men and women, respectively, and the prevalence rates were 132.6 (130.7-134.5) and 70.1 (68.8-71.5) per 100,000 for men and women, respectively. In Sweden, liver cirrhosis incidence was close to that of Denmark, estimated at 15.3 ± 2.4 per 100,000 inhabitants, and did not decrease between 1996 and 2005 [9].

In summary, liver cirrhosis is responsible for 1-2% of all deaths in most European countries according to the WHO database. Increasing or stable incidences of the disease were reported in the published studies (Table 1, page 10). In Mediterranean countries, alcohol consumption and the obesity epidemic threaten to halt the recently-improving trend in liver cirrhosis prevalence, or even to reverse it. Amongst northern European countries such as Denmark and Sweden, liver cirrhosis prevalence has not decreased and still represents a non-negligible factor of morbidity and mortality. Finally, in the UK and Ireland, all studies agreed on the worrying increase in the incidence of liver cirrhosis.

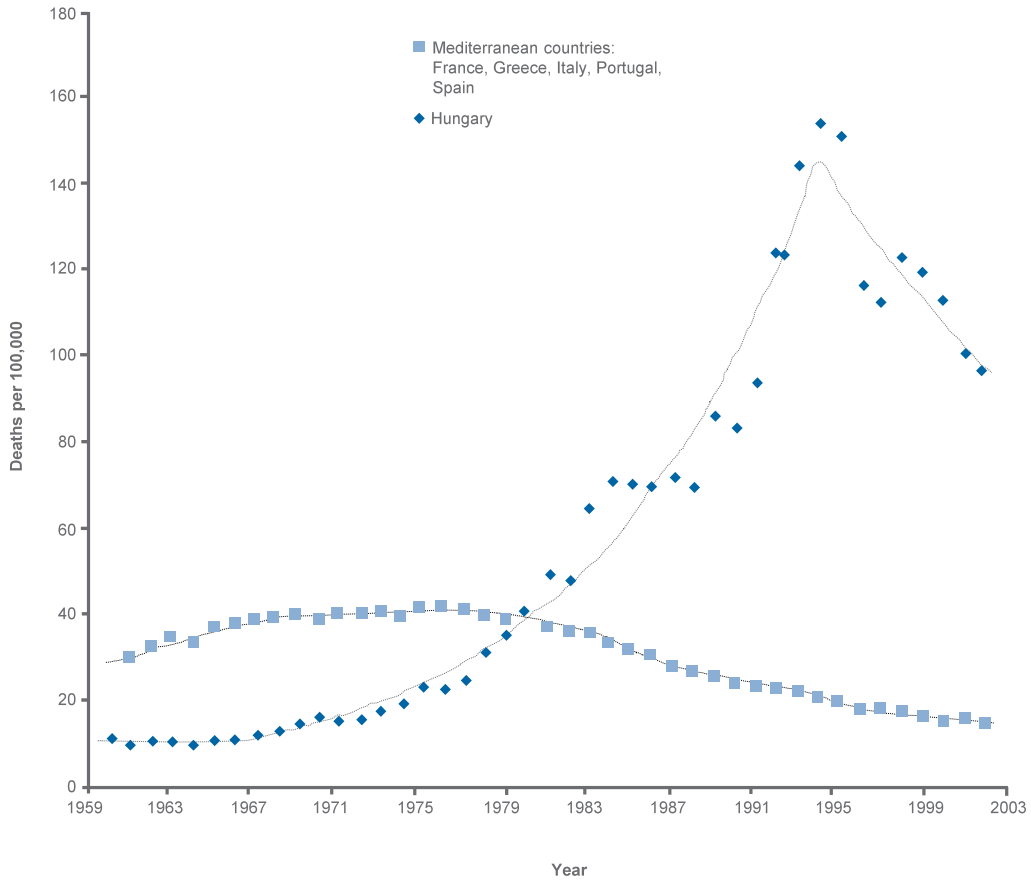

Fig. 1 *– Liver cirrhosis mortality in Mediterranean countries and in Hungary, males 20-64 years, WHO [2].*

Country	Author	Study years and population	Diagnosis	Prevalence or incidence rates (95% CI)	Trends in prevalence or incidence rates
Denmark	Jepsen [8]	1988-2005; alcoholic cirrhosis: a nationwide population-based, hospital registry study	Histology	In 2001–2005, the alcoholic cirrhosis incidence rates were 22.5 (25.7-17.4) and 11.8 (11.2-12.4) per 100,000 per year for men and women, respectively, and the prevalence rates were 132.6 (130.7-134.5) and 70.1 (68.8-71.5) per 100,000	The alcoholic cirrhosis prevalence and incidence rates for men and women of any age did not change significantly from 1996 to 2005
France	Poynard [5]	2006-2008; 7,463 consecutive subjects aged 40 years or older, seen for a free voluntary screening program in two French Social Security health examination centres, 95% male	Histology	The estimated prevalence of fibrosis was 1.3% (1.1%-1.7%) and of cirrhosis was 0.3% (0.2%-0.5%)	
Sweden	Gunnarsdottir [9]	1994-2003; all patients diagnosed with liver cirrhosis in Gothenburg (600,000 inhabitants)	Histology	The mean annual incidence rate per 100,000 inhabitants in Sweden was 15.3 (± 2.4)	The incidence rate and the proportion of alcohol aetiology were fairly constant over the study period
UK	Fleming [6]	1992-2001; the UK General Practice Research Database (GPRD), persons aged 25 and over, 58% male	Any diagnostic or therapeutic code for cirrhosis, oesophageal varices or portal hypertension	Crude incidence was 14.55 per 100,000 person years. Prevalence of cirrhosis was an estimated 76.3 per 100,000 population aged over 25 in mid-2001	The cirrhosis incidence increased from 12.05 to 16.99 per 100,000 person years from 1992 to 2001
UK	Liu [7]	1996-2005; The Million Women Study (an on-going prospective study of 1.3 million United Kingdom women aged 50 and over)	ICD-10 diagnosis code K70, K73, or K74	After a mean follow-up of 6.1 years (1996-2005), incidence rate of cirrhosis was 26 per 100,000 per person-years in women	

Table 1 *– European studies assessing the prevalence or incidence of liver cirrhosis.*

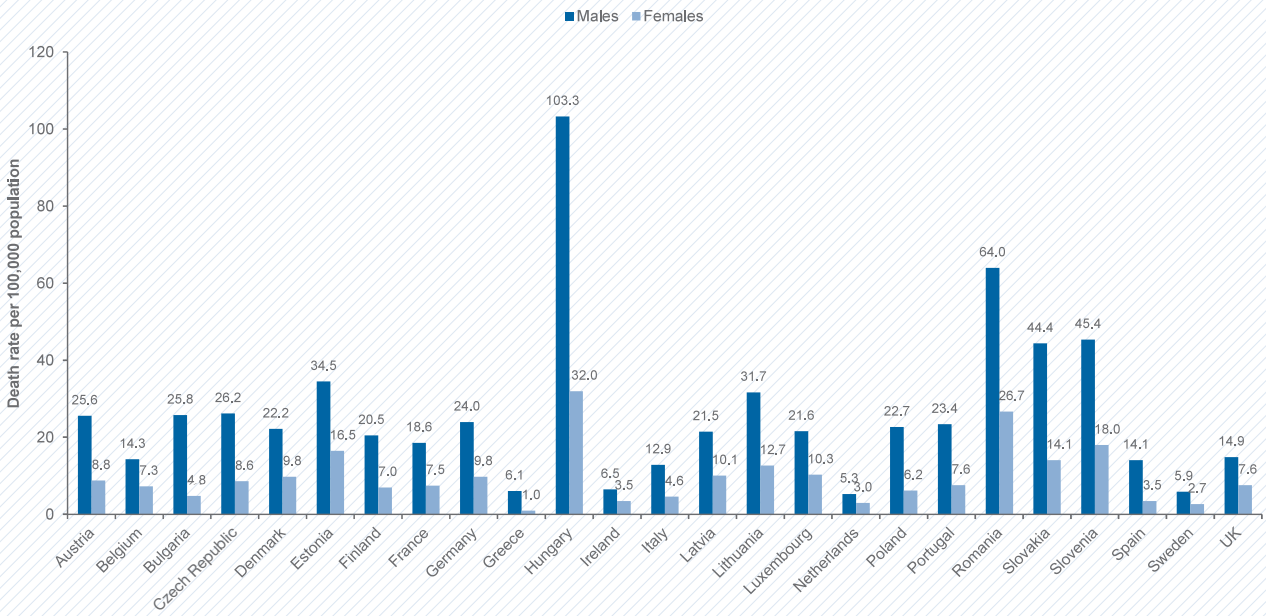

Fig. 2 *– Age-standardized death rates per 100,000 population from liver cirrhosis in European countries, males and females aged 20–64; WHO Mortality Database 2000-2002 [2].*

PRIMARY **LIVER CANCER**

Hepatocellular carcinoma (HCC), accounts for 70–90% of primary liver cancers (PLC). Without any treatment, HCC is rapidly fatal, with a 5-year survival rate of around 5%. When liver resection with curative intention is performed, 5-year survival rates reach 26-40% in French studies [10, 11]. The management of HCC is complicated by the presence of liver cirrhosis in more than 80% of patients. Liver cirrhosis is often the direct cause of death and may hinder cancer treatment. Over half a million new cases of HCC are diagnosed each year worldwide [12-14]. In recent years decreasing incidence has been reported in some high incidence countries, while significant increases have been reported in several low incidence countries [12, 15, 16]. These trends coincide with changes in the consumption of alcohol and the prevalence of HBV or HCV infection, which are major risk factors for HCC [12]. Cancer registry data must be preferred for survey purposes as it is not selective, reporting data for virtually all primary liver cancers. By contrast, clinical studies adopt rigorous selection criteria and are typically performed by tertiary referral hospitals that are likely to be centres of excellence. Clinical studies may provide indications as to the best outcomes possible and usually show better survival than registry data.

Thanks to the GLOBOCAN project (http://globocan.iarc.fr), we have estimates of liver cancer incidence rates for each EU27 country. GLOBOCAN is a project led by the WHO and provides estimates of national rates of incidence, mortality and prevalence for every country in the world, based on national population-based cancer registries and death registration systems. GLOBOCAN 2008 took into account delays in the availability of data by computing predictions of national incidence and mortality rates to the year 2008, wherever possible.

These calculations were based on published data where available or were estimated from national mortality and incidence data or from mortality data provided by local cancer registries. Recent incidence data (up to 2007) were extracted by GLOBOCAN from reports available on the Internet from the national cancer registries in Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Ireland, Luxembourg, Malta, the Netherlands, Slovakia, Slovenia and Ukraine. Data for the five Nordic countries, Denmark, Finland, Iceland, Norway and Sweden, were obtained from the NORDCAN database of the Association of the Nordic Cancer Registries. In the United Kingdom, historical incidence data were available for the populations of England, Scotland and Wales. Additional historical national incidence data for Belarus, Estonia, Latvia and Lithuania, together with local incidence data used for modelling purposes, were extracted from the 'Cancer Incidence in Five Continents' series of monographs published by WHO.

In the EU27 in 2008, liver cancer incidence was 10.6 and 3.6 per 100,000 persons for men and women, respectively [17]. For men, the highest incidence was in Italy (19.9 and 6.8 per 100,000 persons for men and women, respectively) and the lowest was in the Netherlands (2.8 and 1.1 per 100,000 persons for men and for women, respectively) [17]. As expected, estimated mortality rates were very close to incidence rates, indeed the two measures were exactly the same for the EU27 overall [17]. Complete results for all EU27 countries are given on Figs. 3 and 4, page 15.

Few European studies have investigated the incidence of PLC. Those that have were all based on local or national registries (Table 2, page 14). In a study based on three Danish registries, the incidence rate of PLC between 1985 and 2003 was 5.9 (95% CI 5.4–6.3) and 3.7 (95% CI 3.4–4.0) per 100,000 person-years in men and in women, respectively [18]. In the same study, the standardized incidence rate of PLC increased from 3.2 (95% CI 2.2–4.2) to 5.0 (95% CI 3.8–6.2) per 100,000 person-years between 1985 and 2003 [18]. These results were consistent with data from GLOBOCAN which found incidence rates for Denmark in 2008 of 5.8 and 1.9 per 100,000 persons for men and for women, respectively [17]. Three studies published for France estimated PLC incidence rates during the 1990's to be between 9.5 and 13.8 for men and between 0.8 and 1.7 for women [19-21]. GLOBOCAN found similar rates, with 10.5 and 2.2 per 100,000 persons for men and for women, respectively [17]. Finally, in an Italian study based on 20 local registries, the overall standardized incidence rate of PLC was 21.1 per 100,000 person-years in men and 6.0 in women [22]. Rates varied widely among different regions and the results were consistent with those from GLOBOCAN [17].

In summary, PLC rates exceed 10 per 100,000 inhabitants in Southern European countries, reaching 13 per 100,000 in Italy and Greece. It is also common in Germany and Eastern European countries, with incidence rates of 5-10 per 100,000 inhabitants. Unlike other cancers, the mortality rate is very close to the incidence rate because of the very low associated survival rate. Thus, liver cancer is responsible for many deaths in Europe, around 47,000 per annum according to the WHO mortality database. This is lower than the rate for cirrhosis-related mortality (Table 13, page 46).

~ 47,000

Is the number of deaths in Europe caused each year by liver cancer according to the WHO mortality database.

Country	Author	Study year(s) and population	Diagnosis	Standardized incidence rates per 100,000 person-years	Trends in incidence rates
EU27	Ferlay [17], GLOBOCAN	2008; local cancer registries	Histology or clinical and imaging findings	10.6 in men, 3.6 in women	
Denmark	Erichsen [18]	1985-2004; the three Danish counties of North Jutland, Aarhus and Viborg	Histology or clinical and imaging findings	5.9 (95% CI 5.4–6.3) in men, 3.7 (95% CI 3.4–4.0) in women in 1985–2003	Increased from 3.2 (95% CI 2.2-4.2) to 5.0 (95% CI 3.8-6.2) from 1985 to 2003
France	Borie [20]	1997-1998; 9 regional French registries	Histology or clinical and imaging findings	9.5 in men, 1.7 in women	
France	Caumes [21]	2002-2003; the Finistère cancer registry	Histology or clinical and imaging findings	13.8 in men, 0.8 in women	
France	Binder-Foucard [19]	1990-1999; the cancer registry of Bas-Rhin	Histology or clinical and imaging findings	11.7 in men, 1.5 in women	No incidence trend for men or women (p=0.75)
Italy	Dal Maso [22]	1998-2002; 20 Italian cancer registries	Histology or clinical and imaging findings	21.1 in men, 6.0 in women. In Naples, the world-standardized incidence rates for persons aged 0–79 were 29.5 and 8.3 per 100,000 in men and women, respectively, approaching those found in highest risk areas of Asia.	The change in annual incidence rate between 1988 and 2002 was 0.8% in men (95% CI 0.5-2.1%) and 1.1% in women (95% CI 0.2-2.1%).

Table 2 *– European studies assessing incidence of primary liver cancer.*

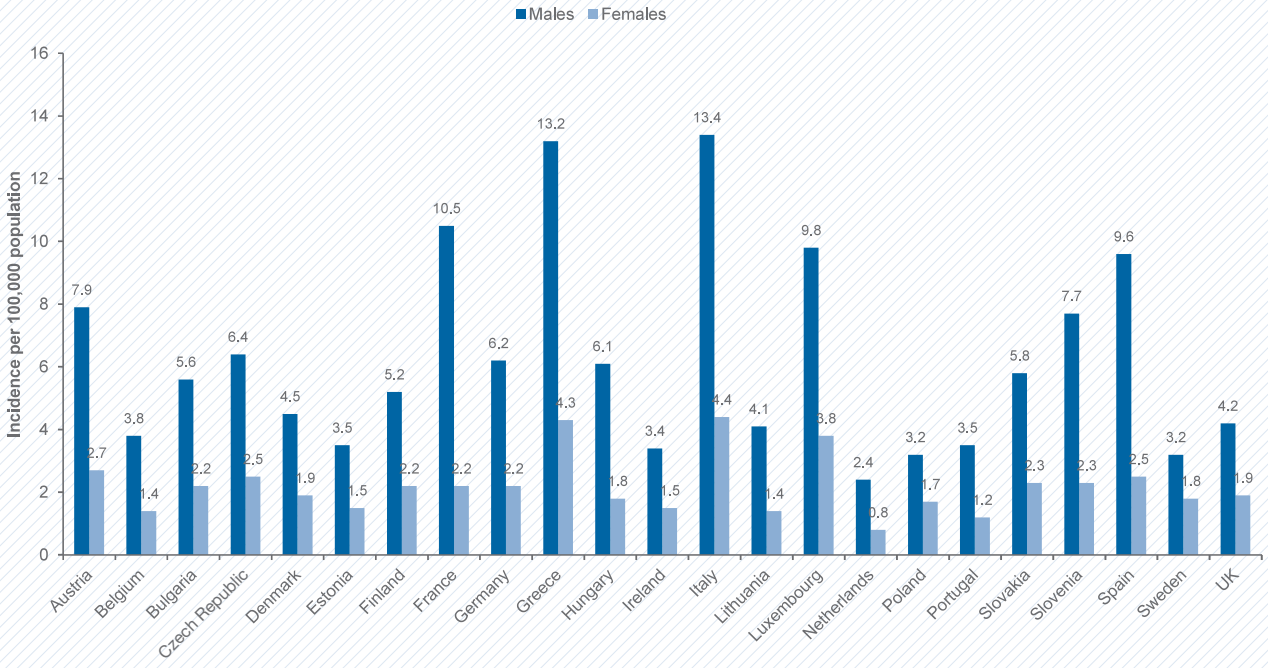

Fig. 3 *– Estimated age-standardized incidence rates of liver cancer per 100,000 in 2008; WHO, GLOBOCAN, 2008.*

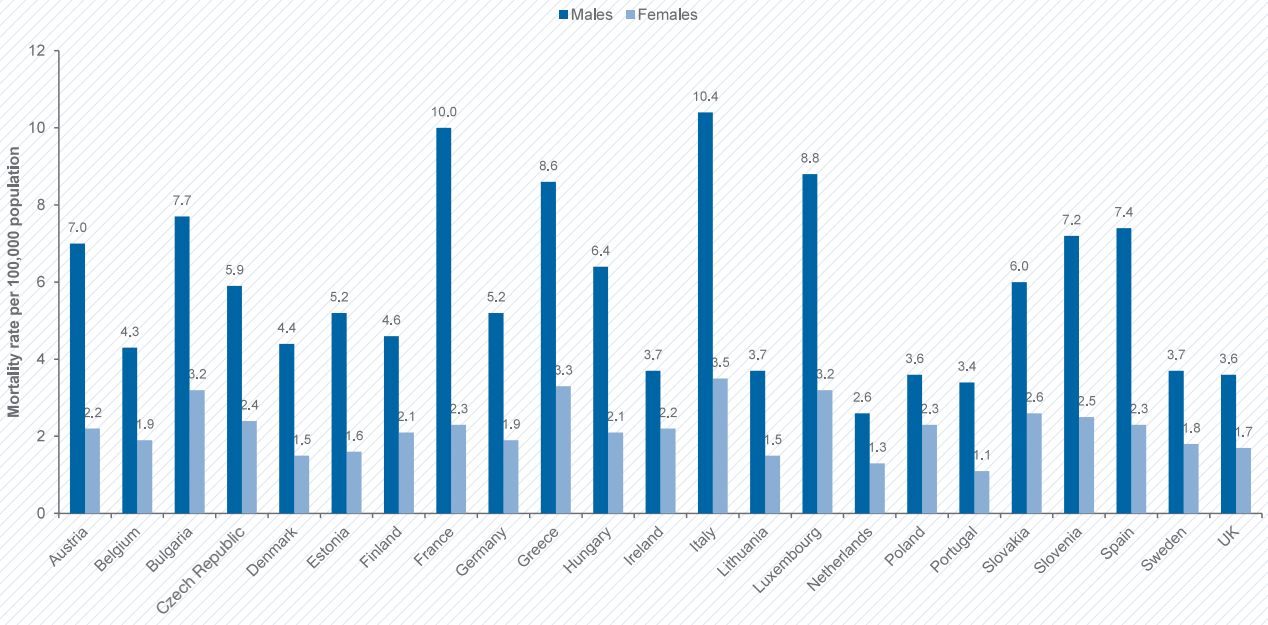

Fig. 4 *– Estimated age-standardized mortality rates per 100,000 for liver cancer in 2008; WHO, GLOBOCAN, 2008.*

LIVER **TRANSPLANTATION**

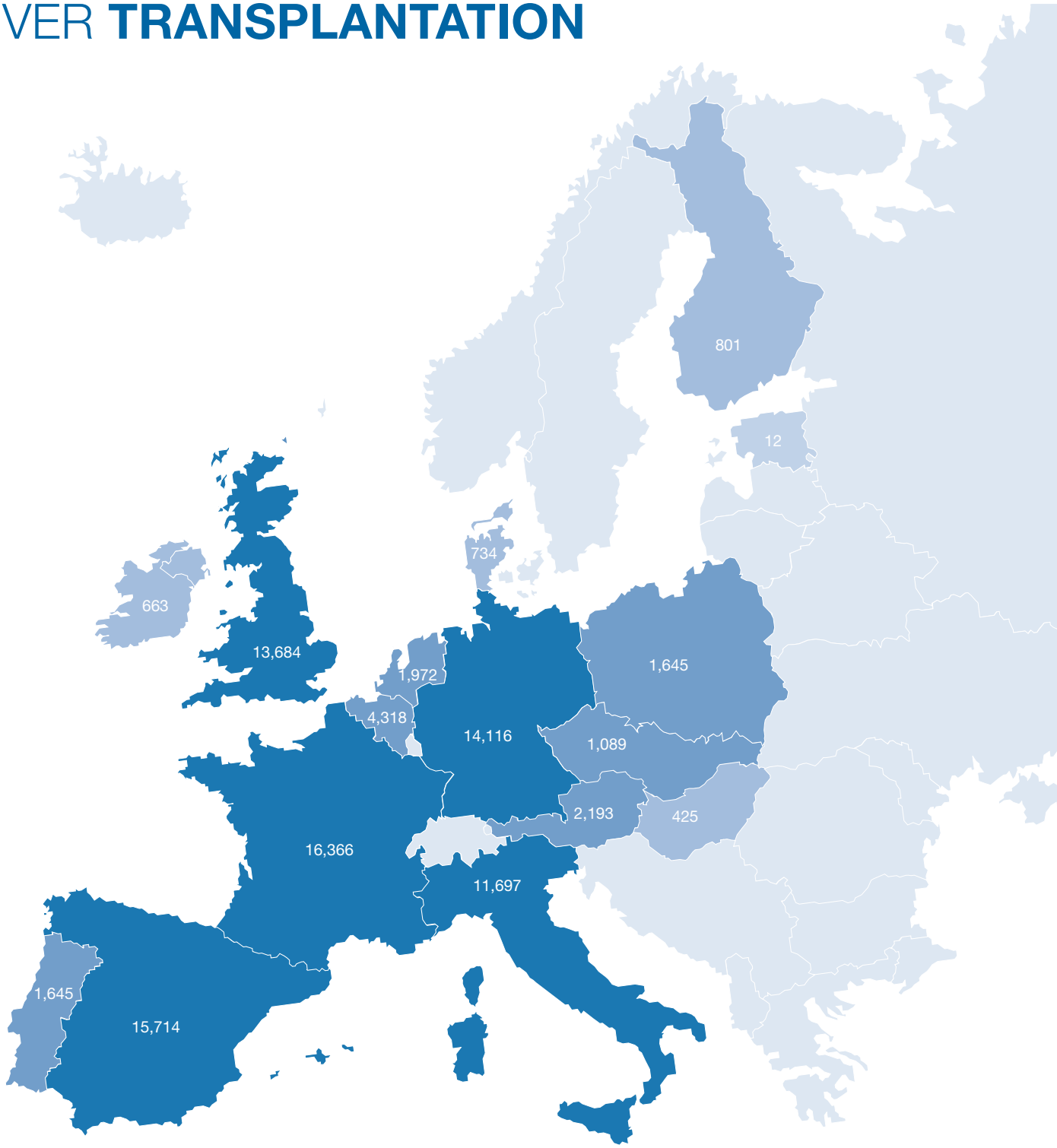

Fig. 5 *– Number of liver transplantations in European countries, May 1968 to December 2009; ELTR [23].*

More than 5,500 orthotopic liver transplantations (OLTs) are currently performed in Europe per year [23]. Figure 5, on page 16, shows the number of OLTs that were performed in 16 European countries between 1968 and 2009. After rapid growth in the 1980s and 1990s, the annual number of OLTs has stopped growing over the last 10 years, limited by the availability of organs (Fig. 6, below). Donor shortage currently represents the most important limiting factor for OLTs [24, 25] and alternatives to standard cadaveric OLTs (a liver from someone that has died), such as split (one liver is divided for two recipients), domino (the original liver from a transplantation patient is transplanted into someone else), or living related (a portion of a healthy person's liver is used) OLTs are increasingly used, accounting for 11% of all procedures [26, 27]. In general, OLTs are considered for any patient with chronic liver disease that leads to life-threatening complications and a survival prognosis of one year or less. The main indications for liver transplantation in Europe are cirrhosis and tumours, mainly related to viruses and alcohol (Figs. 7 and 8, page 18).

Liver transplantation for malignant diseases is feasible, resulting in excellent outcomes in selected patients, and comprises 14% of all liver transplants in the ELTR [23]. It is currently a treatment option for patients with primary carcinomas of the liver, HCC representing 84% of OLTs for cancer. Other types of primary liver carcinomas eligible for transplantation include cholangiocarcinoma, hepatoblastoma, and hemangioendothelioma. The most common secondary carcinomas that are considered for OLT include metastases from carcinoid tumours, neuroendocrine tumours and gastrinomas [28, 29]. Reduced liver, split liver, living donor and domino transplants have been used increasingly in recent years as alternatives to full-size OLT procedures.

One of the most important findings in the evolution of OLTs is the significant improvement in results with time. Currently the 1-year survival rate is reported to be 83% (all indications considered). This improvement is probably due to greater technical expertise, better selection of patients, and improved post-OLT management of complications and immunosuppressive therapy.

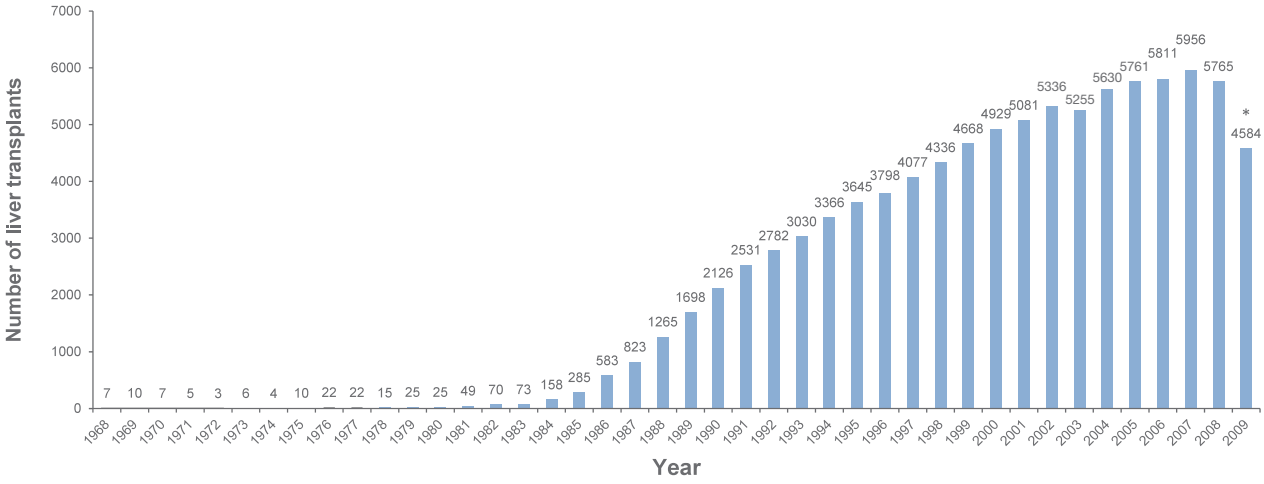

Fig. 6 – *Growth in the annual numbers of liver transplants in Europe.*
** The decrease in 2009 is due to the absence of updated figures from some centres.*

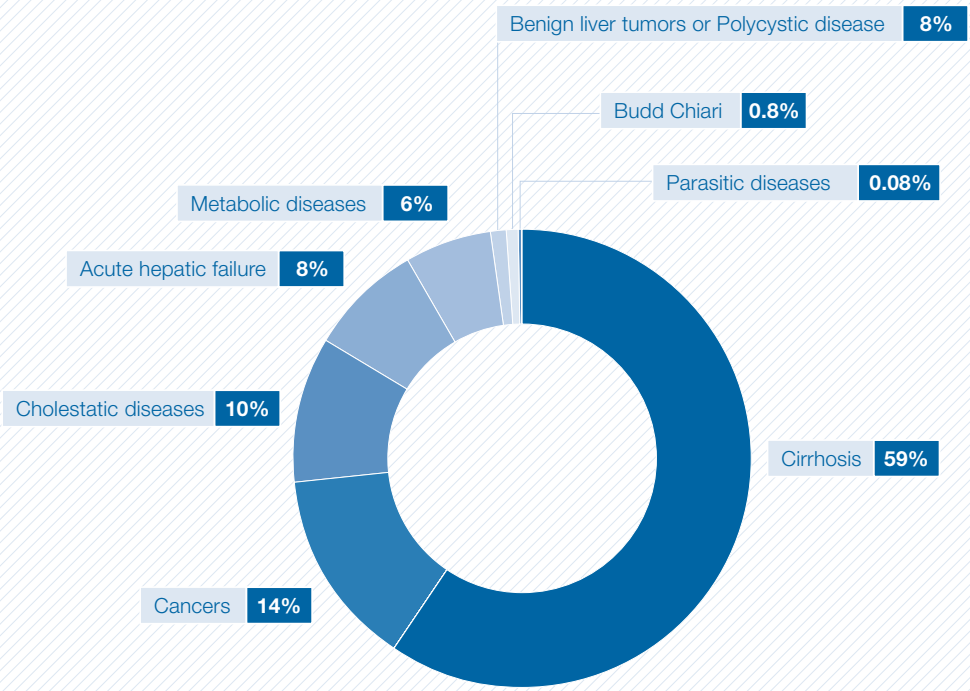

Fig. 7 *– Primary liver diseases leading to liver transplantation in Europe, January 1988 to December 2009.*

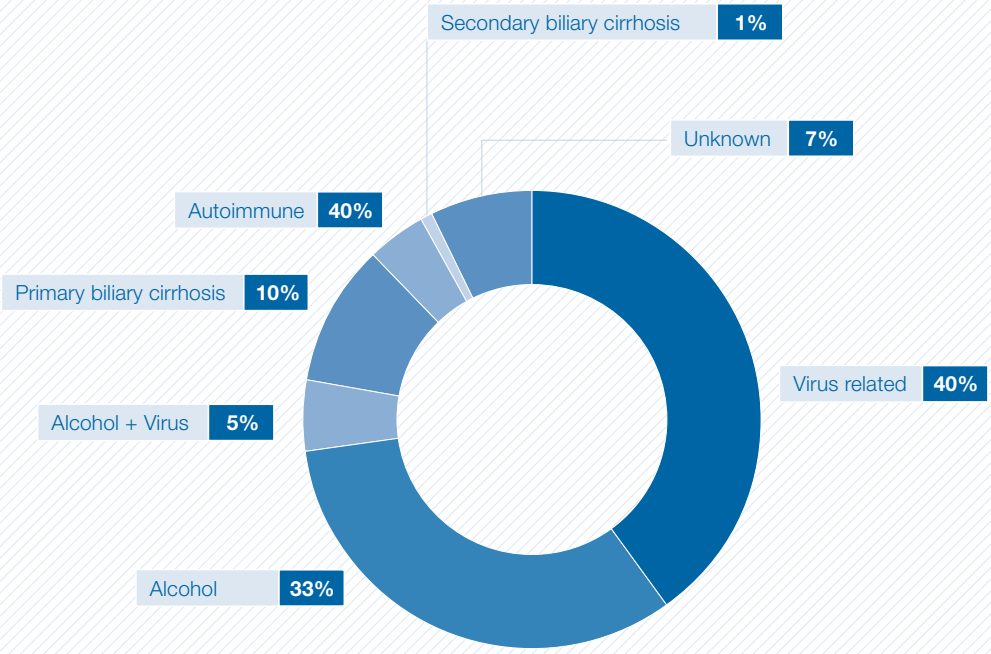

Fig. 8 *– Primary indications for liver transplantation in Europe among patients with cirrhosis, January 1988 to December 2009.*

ALCOHOL AND **LIVER DISEASE**

Europe is the heaviest drinking region in the world in terms of the prevalence of alcohol consumption, according to the WHO report 'European Status Report on Alcohol and Health 2010' [30]. Over 20% of the European population aged ≥15 reported heavy episodic drinking (defined as five or more drinks on one occasion, or 50g alcohol) at least once a week [30].

Alcohol is the main cause of liver disease, including liver cirrhosis (see section on cirrhosis, page 8). The mortality rate associated with cirrhosis has traditionally been considered a good indicator of alcohol-related mortality [2]. Cirrhosis can lead to HCC. In France, excessive alcohol consumption is responsible for 69% of the cases of PLC, making it the main risk factor, although viral aetiology is increasing [20]. An increase in alcohol-related cirrhosis has been observed in Estonia [31] and in Denmark [32] in the last decade, in line with increases in alcohol consumption in the 1990s in those countries.

Standardized mortality rates for alcohol-related liver diseases among men and women during 2000-2005 are available for 24 European countries, based on death certificates (Fig. 9, below and Fig. 10, page 20). They show a significant impact of chronic alcohol consumption on health in Europe, though the figures vary greatly between countries, ranging from 3 per 100,000 men in Latvia to more than 47 per 100,000 men in Hungary. However, this data needs to be interpreted cautiously as there is variability between countries in the way mortality is declared and how alcohol related diseases are recorded in death certificates. Nevertheless, when considering alcohol consumption (Fig. 11, page 20) and alcohol related mortality (Figs. 9 and 10) simultaneously, countries on the lower end of both figures (e.g. Norway or Sweden) give an indication of what could be achieved in terms of mortality reduction should proper alcohol policies be implemented.

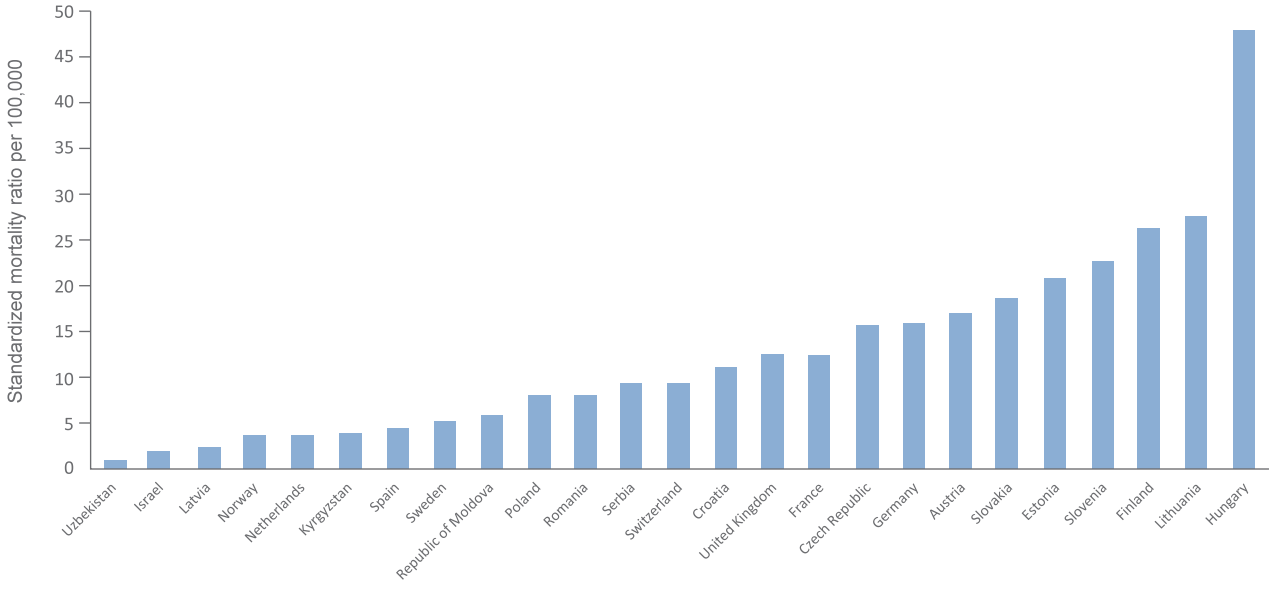

Fig. 9 *– Mortality from alcohol-related liver diseases among men in European countries in 2005; WHO 2010 [30].*

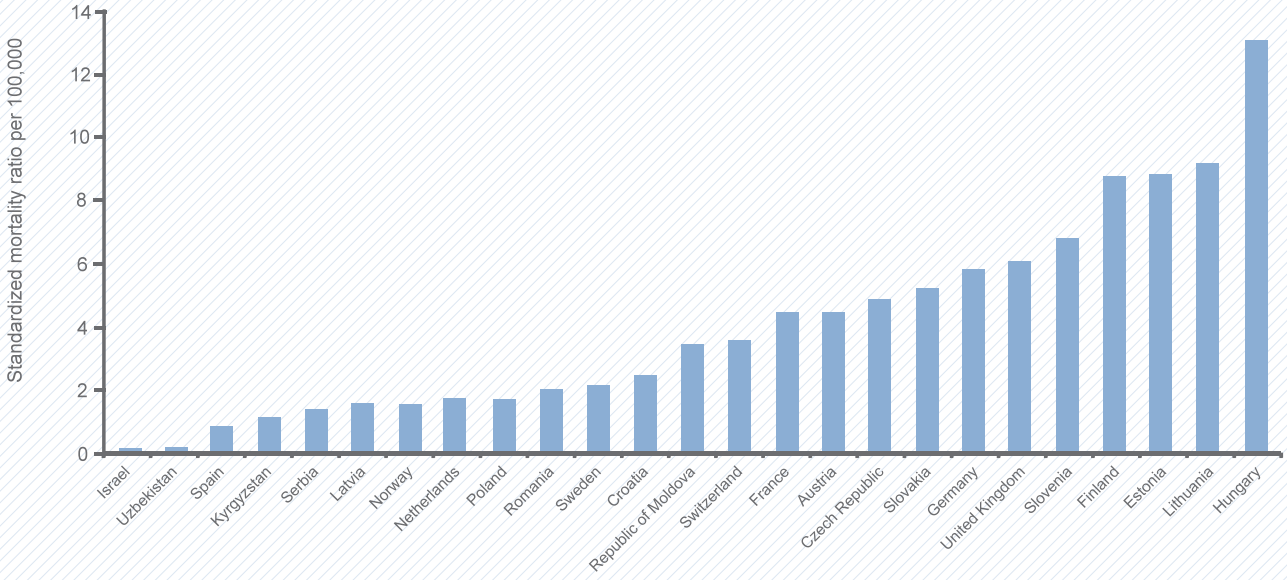

Fig. 10 *– Mortality from alcohol-related liver diseases among women in European countries in 2005, WHO 2010.*

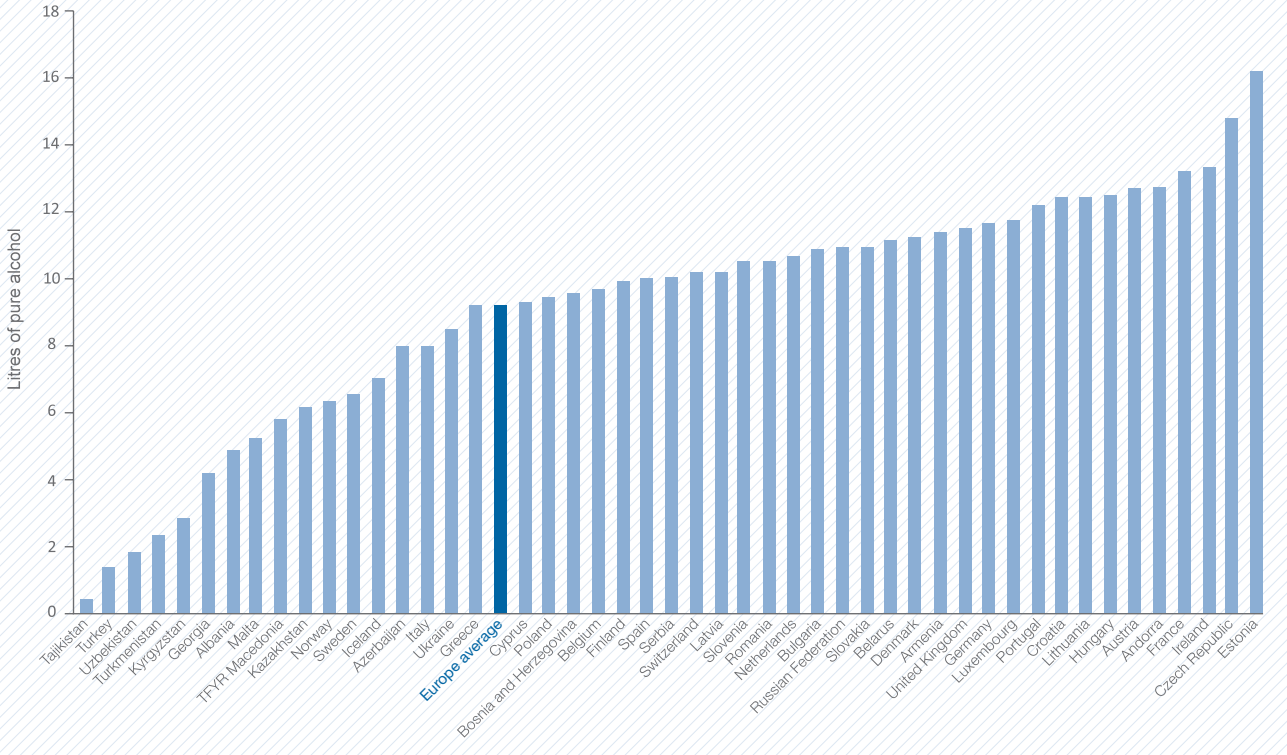

Fig. 11 *– Alcohol consumption in Europe in 2005: WHO.*

Data on the acute consequences of alcohol consumption are scarce. From 1999 to 2008, the annual incidence rate of alcoholic hepatitis in the Danish population rose from 37 to 46 per 100,000 for men and from 24 to 34 per 100,000 for women, according to an epidemiological study of a national cohort. The 5-year mortality was 47% without cirrhosis, 69% with cirrhosis and 56% overall [33].

Trends in alcohol consumption over the last two decades, estimated from surveys in each member state as well as from alcohol industry statistics, showed a decrease during the 1990s.

This was followed by an increase and stabilization at a higher level between 2004 and 2006 (Fig. 12, below). There are huge variations in alcohol consumption among European countries (Fig. 11, page 20). The burden of liver disease attributable to the use of alcohol is significant compared to other aetiologies. Moreover, in many countries alcohol consumption causes substantial health, social and economic burdens, not only in relation to public health problems including liver and psychiatric disease but also in terms of accidents and alcohol-related violence.

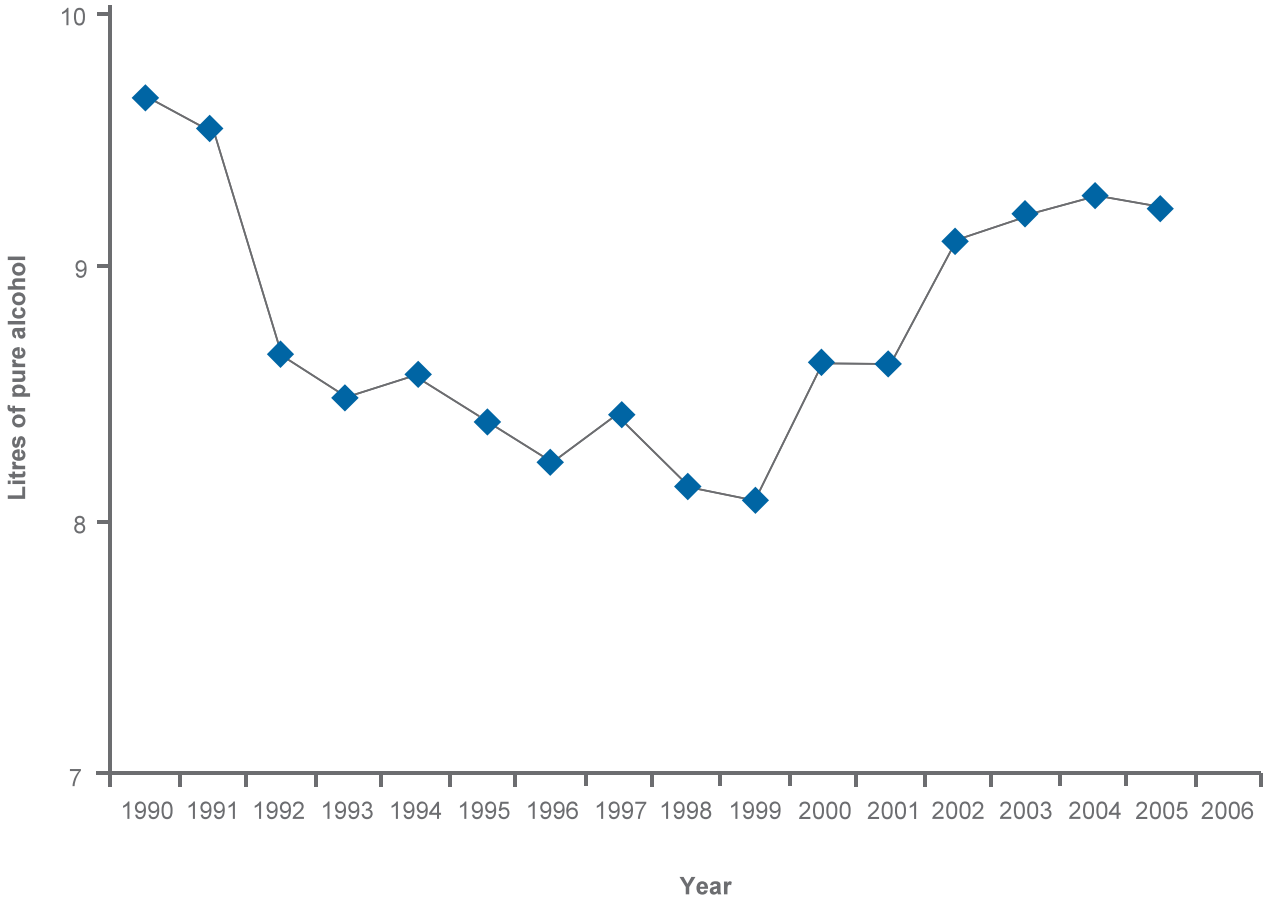

Fig. 12 *– Alcohol consumption in Europe between 1990 and 2006; WHO 2010 [30].*

HEPATITIS A

Hepatitis A is caused by infection with the hepatitis A virus (HAV). It has an incubation period of approximately 28 days and is primarily transmitted by the faecal-oral route, either by person-to-person contact or consumption of contaminated food or water. HAV infection does not result in chronic infection or chronic liver disease. Manifestations of infection vary with age. Most infected adults have a symptomatic form whereas most infections in children are asymptomatic or unrecognized. About 0.5 % of cases of hepatitis A will result in acute liver failure and death, but mortality reaches up to 2.1% in adults over 40. HAV antibodies persist for many years after the infection has resolved, providing long term immunity [34]. HAV vaccines are available today and are routinely used in European countries for populations and travellers at risk. The picture of HAV epidemiology has changed in Europe over past decades because of improvements in hygiene and sanitation, coupled with economic and social advancement. Most European countries have observed a dramatic drop in the level of hepatitis A incidence, and a shift in the age-specific seroprevalence rates (Table 3, page 23 and Table 4, page 24). As a consequence, a smaller fraction of the population is immune, especially early in life when HAV infection is mainly asymptomatic. The yearly incidence rate of hepatitis A in Europe today is between 0.55 and 1.5 cases per 100,000 inhabitants, based on data from epidemiological surveillance systems (Table 3) and there are large differences between European countries. Hospitalization rates for HAV infection range from 0.2 per 100,000 inhabitants in the Netherlands to 94 per 100,000 in Romania (Fig. 13, below).

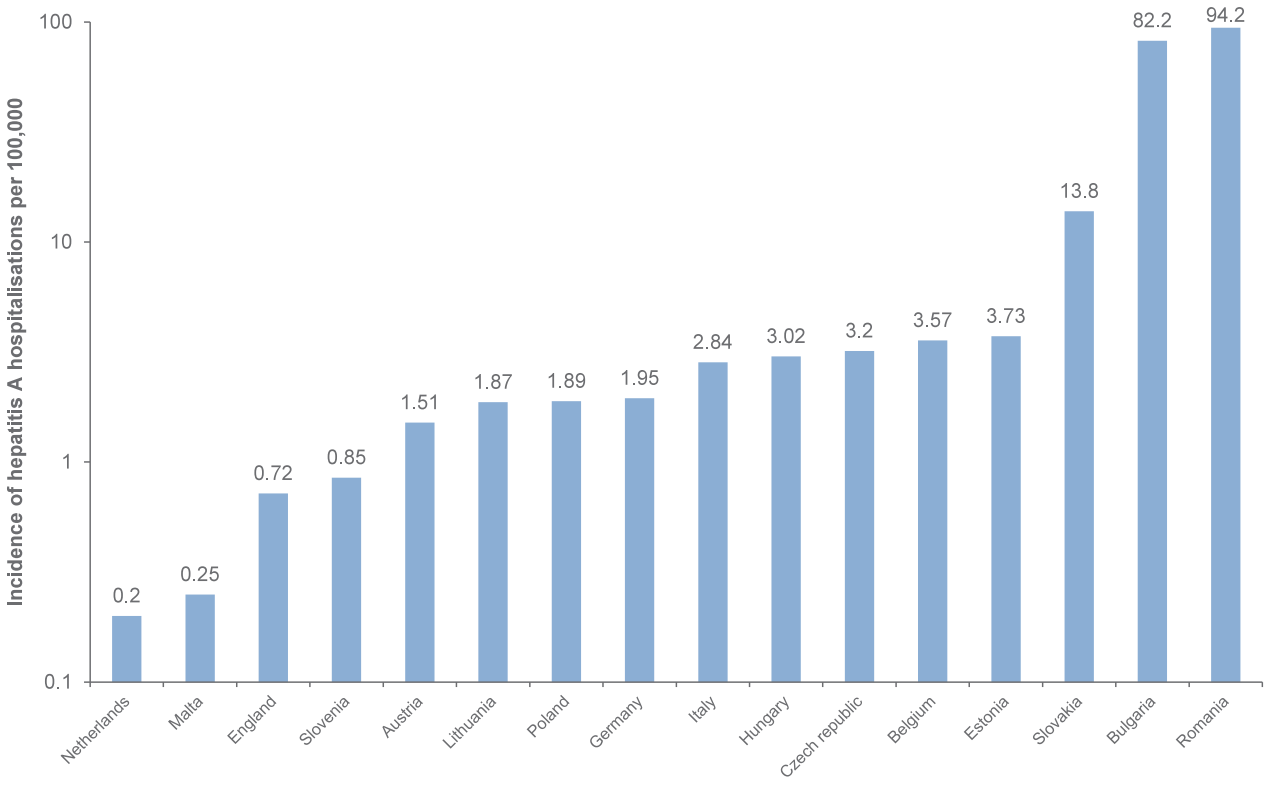

Fig. 13 *– Hospitalisation for hepatitis A, incidence per 100,000 inhabitants in Europe; EUROHEP.NET.*

Declining HAV incidence and seroprevalence have delayed the age at which individuals become infected until adulthood, at which time the likelihood of developing the symptomatic illness is considerably higher. Several countries have considered systematic vaccination because of the greater disease burden of late HAV infections. These vaccination programs have shown to be effective in reducing incidence, outbreaks, mortality rates and hospitalisation [35]. One strategy is to combine HAV and hepatitis B virus (HBV) vaccination. Cost-effective analyses performed in Ireland showed vaccination to be the strategy of choice where HAV immunity is 45% or less [36].

HAV still poses a serious threat to public health in Europe, despite declining incidence, because reduced population protection leads to more symptomatic cases and to outbreaks. Epidemics were responsible for a 10-fold increase in the incidence rate in the Czech Republic in 2008 [37, 38] and an incidence rate of 124 per 100,000 inhabitants in Latvia in 2008 [39]. Two epidemics reported in Finland in 1994-1995 and 2002-2003 started with intravenous drug users and spread to the rest of the population [40]. Luyten et al. have estimated that a HAV outbreak can have a major economic impact, ranging from USD 3,824 to USD 200,480 per case [41].

Country	Author	Study year(s) and population	Case identification	Incidence rates per 100,000	Trends in incidence rates
Czech Republic	Fabianova [38]	2003-2007; general population	Mandatory case declaration	1.48	
Italy	Tosti [42]	2006; general population	Epidemiological surveillance system	1.4	Decreased from 4.0 in 1991
Netherlands	Suijkerbuijk [43]	2005; general population	Mandatory case declaration	1.3	Decreased from 6.5 in 1995
Poland	Baumann [44]	2007; general population	Mandatory case declaration	0.09	A decrease of 31% compared to 2006 (part of a downward trend since 1997)
Poland	Baumann [45]	2008; general population	Mandatory case declaration	0.55	Increased from 0.09 in 2007
Spain	Arteaga [46, 47]	2008; general population	Hospitalisation	1.36	Decreased from 1.87 in 2005

Table 3 – *Incidence rates of HAV infection in Europe.*

Country	Author	Study year(s) and population	Diagnostic method	Prevalence rates (95% CI)	Trends in prevalence rates
Belgium	Quoilion [48]	2007; general population	Oral (saliva) testing for antibodies	20.2% (19.43 – 21.08) weighted for age	
Finland	Broman [40]	1990-2007; patient sample	Oral (saliva) testing for antibodies	30-45%*	
Greece	Kyrka [49]	2008; unvaccinated children 0-14 years old	Oral (saliva) testing for antibodies	17.1%	
Italy	D'Amelio [50]	2005; military recruits	Oral (saliva) testing for antibodies	5.3%	Decreased from 66.3% in 1981 to 29.4% in 1990

*Finland has a HAV vaccination program

Table 4 *– Prevalence rates of HAV infection in Europe.*

HEPATITIS B

Hepatitis B is caused by infection with the hepatitis B virus (HBV). Primary risk factors for HBV transmission are sexual contact, percutaneous exposure to infectious body fluids, perinatal exposure to an infected mother and prolonged close personal contact with an infected person [51]. Acute HBV infection is symptomatic in 30-50% of adults over 5 years, with a case-fatality of approximately 1% [52]. The risk of HBV infection becoming chronic is 90% for infants, 30% for infected children aged <5 years and 2-6% for adults [53]. Chronic HBV infection is rarely symptomatic in adults. HBV has sometimes been called 'the silent killer' because infected adults often remain undiagnosed and thus untreated until it is too late. Throughout Europe, an average of only 23% of patients knew of hepatitis B at the time of their diagnosis and only 27% knew they were at risk of contracting it [54]. In a French study of HBV infection, 18% of identified patients were detected by standard testing during pregnancy [55]. Universal (targeting specific age-cohorts) vaccination strategies deployed in many European countries have achieved high coverage rates among infants and adolescents [56].

The yearly incidence of new cases of HBV shows large variation from 0.2 to 11.2 cases per 100,000 inhabitants in France and Iceland, respectively (Fig. 14, page 26).

The prevalence of chronically HBV-infected patients has been estimated from hepatitis B surface antigen (HBsAg) identification in sera collected from the general population in several European countries (Table 5, page 26). Prevalence estimates range from 0.1 to 0.7%, with the exception of Romania (5.6%) and Greece (3.4%) (Table 5 and Table 7, pages 26 and 27).

Chronic HBV infections translate into a heavy disease burden in Europe. Cirrhosis occurs in 20 to 30% of infected patients [55, 57] with about 25% at risk of developing hepatocellular carcinoma, thus HBV is responsible for 10-15% of primary liver cancers [58]. HBV infections also translate into excess mortality risk. Estimation from mortality registers suggests that HBV infected patients have an excess risk of all-cause mortality and liver-related mortality [59]. About 46% of this excess liver-related mortality is explained by liver cancer. HBV infection is responsible for a mortality rate of 2.7 and 2.5 persons per 100,000 inhabitants per year in Spain and France, respectively [60, 61].

The available data suggest there has been a reduction in yearly incidence of HBV, accompanied by a decline in prevalence related to the vaccination campaigns that have been mounted throughout Europe (Table 6 and 7, page 27) [62, 63]. However, a lack of reliable epidemiological data on HBV is one of the biggest obstructions to the development of policies for its management. For example, surveillance data collected by the European Centre for Disease Prevention and Control (ECDC) must be interpreted with caution because of the absence of a standardized definition of HBV infection.

Despite vaccination and decreased incidence, HBV infection remains a public health issue with many patients unaware of their HBV status. Those patients are faced with many complications including cirrhosis and liver cancer, leading to increased mortality rates.

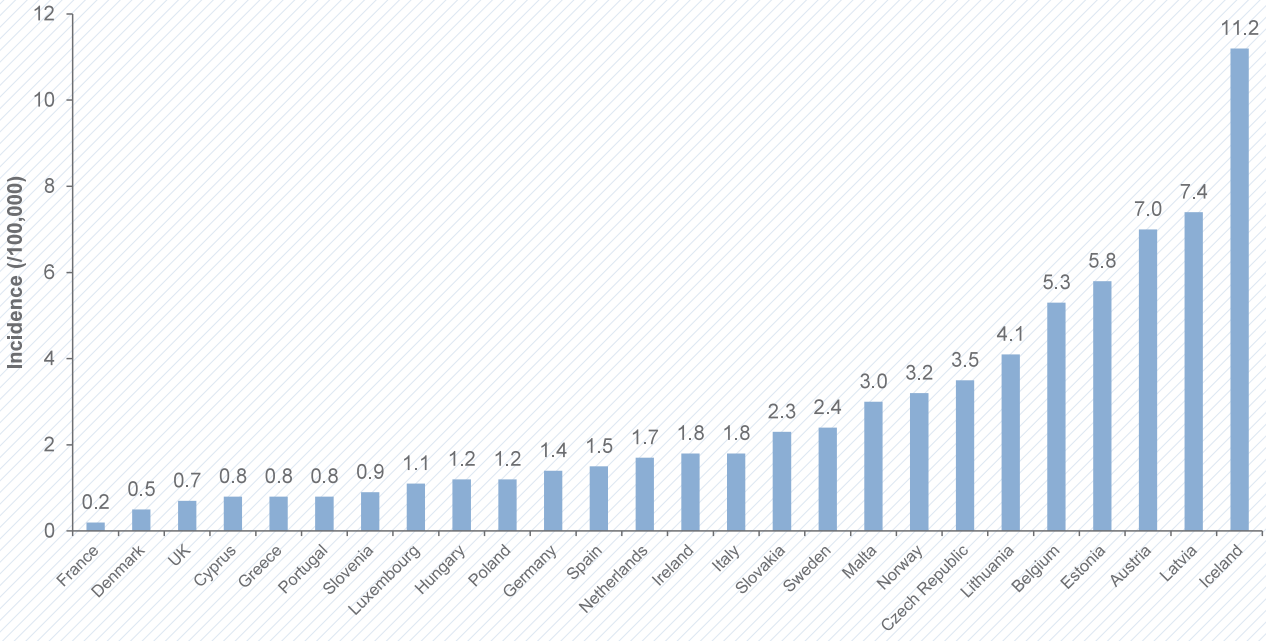

Fig. 14 *– Incidence rates of hepatitis B in EU27 countries in 2005; ECDC 2007.*
Caution: *there is no of standardized definition of new HBV cases; sometimes reactivations are included.*

Country	% anti-HBC	% HBsAg
Belgium	1.3	0.7
Czech Republic	2.5	0.3
Germany	6.0	-
Italy	5.6	0.6
Luxembourg	2.9	-
Romania	20.5	5.6
Slovakia	10.5	0.6
Finland	2.7	0.2
Ireland	1.7	0.1
Netherlands	1.7	0.1
France*	7.0	0.65

*Data added from Institut de Veille Sanitaire, 2004 [65]

Table 5 *– Age-specific HBV seroprevalence in European countries [64].*

Country	Author	Study year and population	Case identification	Incidence rates per 100,000	Trends in incidence rates
Poland	Czarkowski [66, 67]	2006; general population	Mandatory declaration	4.4	Stable since 2005 when the rate was 4.5
Romania	Pitigoi [68]	2004; general population	Mandatory declaration	8.5	Decreased from 43 in 1989

Table 6 *– HBV incidence in Europe.*

Country	Author	Study year and population	Diagnostic method	Seroprevalence	Trends in seroprevalence
Belgium	Quoilin [48]	2006; general population	HBs antigen testing in saliva	0.66%	
France	Meffre [69]	2004; general population	HBs antigen testing in serum	0.65%	
Greece	Zacharakis [63]	2006; general population	HBs antigen testing in serum	3.4%	Decreased from 5.4% in 1994
Greece	Papaevangelou [70]	1998; children	HBs antigen testing in serum	0.6%	
Italy	Fabris [71]	2007; general population in northern Italy	HBs antigen testing in serum	1%	
Netherlands	Baaten [72]	2004; general population in Amsterdam	HBs antigen testing in serum	0.4%	
Romania	Voiculescu [73]	2009; general population SE Romania	HBs antigen testing in serum	5.6%	
Spain	Salleras [74]	2002; general population in Catalonia	HBs antigen testing in serum	0.7% (0.4-1)	Decreased from 1.5% in 1989

Table 7 *– Seroprevalence of chronically HBV-infected patients in Europe.*

HEPATITIS C

Hepatitis C is caused by infection with the hepatitis C virus (HCV). HCV is transmitted through percutaneous exposure to infected blood, e.g. through intravenous drug use, transfusion [75, 76] and medical procedures [77, 78]. About 90% of HCV infection remains asymptomatic. In Europe, a significant number of persons acquired hepatitis C virus in the 1970's and 1980's before the virus was identified and a diagnostic test was available. Since then, the transmission of infection has been greatly reduced and it is now mainly concentrated in intravenous drug users. However the disease has a prolonged time-course, individuals developing cirrhosis within 20 years [79], and so the disease burden of HCV in Europe is at its peak only now.

There is a lack of reliable epidemiological data on HCV in Europe [80]. An annual average incidence rate of 6.19 per 100,000 inhabitants (95% CI 4.90-7.48) can be estimated, based on rates reported from the European region to the WHO [80]. Available literature suggests that the overall prevalence in Europe, estimated from serum antibodies, varies between 0.12% and 3.23% (Table 8, page 29). This accords with the 0.003 % to 4.5% prevalence rate reported by WHO for the wider European region (as geographically-defined by WHO) [80]. Intravenous drug users are particularly exposed to the risk of HCV infection, with prevalence rates of up to 50% in Cyprus [81], 59.8% (95% CI 50.7-68.3) in France [82], 75% for those admitted for opiate detoxification in Germany and 83.2% in Italy [83].

Studies on the natural history of the disease show that up to 85% of infected patients develop a chronic infection, with 10 to 20% progressing to cirrhosis [75]. About 7% of cirrhosis patients will develop hepatocellular carcinoma (HCC) [84] and HCV is an important risk factor for this cancer [58]. HCV is the main indication for virus-related liver transplantation (Fig. 15, page 29). Current studies in patients diagnosed with hepatitis C show increased morbidity, with higher hospital admission rates [85] and mortality rates three times higher than that of the general population, due to both drug use and liver disease [86]. It is estimated that there are 2.5 HCV-associated deaths per 100,000 inhabitants in France, 95% with cirrhosis and 33% with HCC at death [61]. In Spain, the mortality rate due to HCV infection is 11.25 per 100,000 inhabitants [60]. Cost analysis, including the cost of complications, shows that the median lifetime cost for treating one patient with dual therapy (pegylated interferon and ribavirin) is between EUR 7,517 and EUR 21,229, depending on the virus genotype [87]. In cost effectiveness analyses of new protease inhibitors for treating chronic hepatitis C universal triple therapy costs an additional USD 70,100 per quality-adjusted life year (QALY) (mild fibrosis) and USD 36,300 QALY (advanced fibrosis) compared with standard pegylated interferon plus ribavirin therapy [88].

Models suggest that HCV-related morbidity will rapidly increase in the short-term. In the UK, models based on the natural development of HCV and on epidemiological data suggest that HCV-related cirrhosis and death from HCC are likely to increase dramatically in the next decade, reflecting the increased incidence of HCV infection in the early 1980's [89]. A recently published model suggests that treatment with pegylated interferon and additional effects of triple therapy with a protease inhibitor could reduce HCV genotype 1-related cumulative incidence by 17.7% and mortality by 9.7% between 2012-2021 [90].

Although HCV transmission has been greatly reduced and prevention strategies have been effective [91], the issue of patients now chronically infected with HCV needs to be addressed as these patients will represent a heavy disease burden in the coming years.

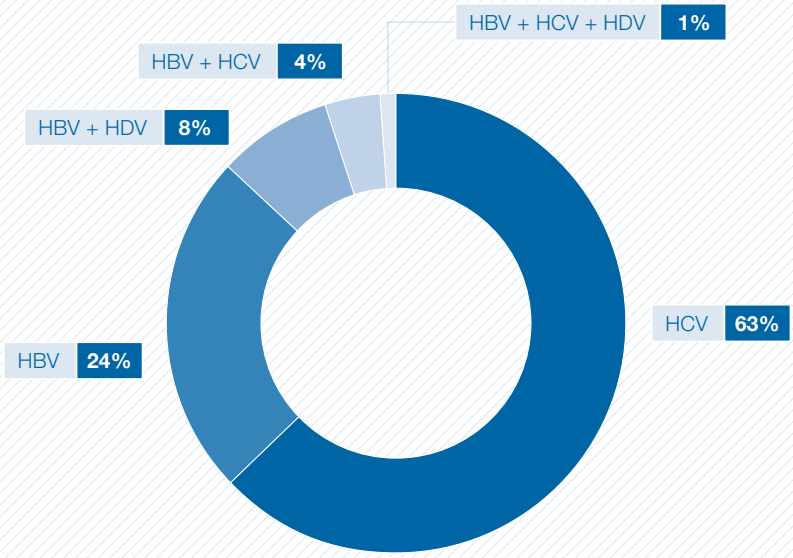

Fig. 15 *– Primary indications for liver transplantation in Europe among patients with virus-related liver disease (January 1988 to December 2009).*

Country	Author	Study year and population	Case identification	Prevalence	Trends in prevalence
Belgium	Quoilin [48]	2007; general population	Anti-HCV testing in saliva	0.12%	
France	Meffre [69]	2004; general population	Anti-HCV testing in serum	0.65%	
France	Delarocque-Astagneau [91]	2004; adults aged 20-59	Anti-HCV testing in serum	0.71%	Decreased from 1.05% in 1994
Italy	Cozzolongo [92]	2007; southern Italian town	Anti-HCV testing in serum	2.6%	
Italy	Fabris [71]	2008; nothern Italy	Anti-HCV testing in serum	2.6%	
Netherlands	Baaten [72]	2004; general population	Anti-HCV testing in serum	0.6%	
Romania	Gheorghe [93]	2008; general population	Anti-HCV testing in serum	3.23%	

Table 8 *– HCV prevalence in Europe.*

HEPATITIS D

Hepatitis delta virus (HDV) is a small, defective RNA virus. It can infect only an individual who has also been infected by HBV, either after concomitant transmission of the two viruses (so called co-infection), or via a subsequent infection of a HBV infected patient (so-called super-infection) [94]. HDV co-infection may cause a benign, self-limited disease. However, it has been consistently shown that most patients with HBV and HDV co-infection develop chronic infection and have more severe liver disease [95, 96], more rapid progression to cirrhosis [97, 98] and increased hepatic decompensation, and death [99] compared with patients who have chronic HBV infection alone.

The highest prevalence is seen in central Africa, the Horn of Africa, the Amazon Basin, Eastern and Mediterranean Europe, the Middle East, and parts of Asia [100]. However, prevalence rates are also high in some Eastern European countries. Most of the cases recorded in other European countries are found in populations originating from endemic regions. Limited data are available for basing an estimate of HDV prevalence in European countries.

Among 16,597 HIV patients enrolled in EuroSIDA, 61 of 422 (14.5%) HBsAg-positive carriers were anti-HDV-positive. HDV predominated in intravenous drug users and in southern and/or eastern Europe. Serum HDV-RNA was detectable in 87% of anti-HDV-positive patients [101].

In Switzerland the prevalence of HDV infection in 1,699 patients with chronic hepatitis B was 5.9% [102]. For two decades (1989 to 2008), 1,307 HBsAg carriers were followed for a mean of 7 ± 6 years at Düsseldorf University hospital. Hepatitis D prevalence increased from 4.1% to 6.2% among HBsAg carriers during the two decades ($p < 0.06$). The proportion of patients originating from the former Soviet Union (32.1 vs. 46.2%) and Africa (0 vs. 17.9%) increased whereas the proportion of patients from southern Europe decreased (46.5 vs.17.9%; $p < 0.03$).

Estimated survival and complication-free survival during 12 years were 72% and 45% in cirrhotic patients compared to 100% in non-cirrhotic patients ($p < 0.008$ and $p < 0.0001$, respectively) [103].

Among 737 patients from a large cohort of HBsAg-positive patients in central Italy, 4.2% and 17% of Italian patients and patients from outside of the EU, respectively, had anti-HDV antibodies [104]. The prevalence of HBV and HDV in Liguria, Italy (1,572,000 inhabitants), was assessed in a network of 12 referral centres for liver diseases. All patients with HBsAg followed throughout 2006 were included. 445 (71% male) were evaluated, in whom the prevalence of HDV infection was 5.7% [105]. In southern Italy, 1,336 HBsAg positive subjects consecutively observed in 79 Italian hospitals were evaluated over a 6-month period. The proportion of patients co-infected with HDV was 9.7% [106].

A retrospective analysis of 962 consecutive HBV-infected adult patients referred to King's College Hospital in London was performed between January 1st 2000 and March 31st 2006. Excluding non-UK residents, the prevalence of anti-HDV antibodies was 7.1%. Most HDV-infected subjects were born in regions where HDV is endemic, for example southern or eastern Europe (28.1%), Africa (26.8%) or the Middle-East (7.3%) [107].

87%

Percentage of serum HDV-RNA detected among anti-HDV-positive patients.

HEPATITIS E

Hepatitis E virus (HEV) is the causative agent of an acute form of hepatitis identified in 1983. Infection in severely immunocompromised patients produces a chronic form of the disease. Hepatitis E is also known to cause infections in animals, particularly, but not exclusively, in pigs. Epidemics have occurred regularly in many countries across south and southeast Asia and in Africa. Although hepatitis E has been reported from many European countries [108], its incidence in Europe is largely unknown, and the seroprevalence of HEV infection is also unknown for most countries in this region.

Three studies investigated the prevalence of HEV infection in Spain. Anti-HEV antibodies were detected in fifty samples (2.17%) of 2,305 serum samples taken from the general population (aged 2-60 years) in Madrid [109]. In a representative sample of 1,249 healthy children from North-Eastern Spain aged between 6 and 15 years; anti-HEV antibodies were detected in 57 (4.6%) children, suggesting that some children are exposed to HEV in early childhood [110]. In a community-based seroepidemiological survey of HEV infection in Catalonia, anti-HEV antibodies were detected in 96 (7.3%) of the 1,280 samples analysed [111].

Two studies provide estimations of the prevalence of HEV infection in Switzerland. Among 735 HIV-infected patients with unexplained alanine aminotransferase elevation the prevalence of anti-HEV antibodies was 2.6% [112]. Among 550 consecutive blood donor samples collected in the region of Lausanne, anti-HEV antibodies were found in 27 (4.9%). The seroprevalence was 5.4% (18/332) in men and 4.1% (9/218) in women [113]. In southwest France the prevalence of anti-HEV antibodies among 529 samples from rural and urban blood donors was 16.6%, (19.1% in rural donors and 14.2% in urban donors) [114]. In the Paris area, the prevalence of anti-HEV antibodies in blood donors was 3.2% [115].

Among 184 patients infected with HIV in Marseille, the prevalence of serum anti-HEV antibodies and HEV RNA was 4.4% (8/184) and 1.6% (3/184), respectively [116].

In Italy, 92 workers at risk from zoonoses and 3,511 controls from the general population of Rome and Rieti were tested for anti-HEV antibodies. The prevalence was 2.9% in the general population compared with 3.3% among pig breeders. The prevalence in subjects recruited in Rome and Rieti was 2.5% and 5.5%, respectively ($p = 0.0004$) [117].

1983

Year when Hepatitis E virus (HEV) was identified.

NON-ALCOHOLIC **FATTY LIVER DISEASE (NAFLD)**

NAFLD is defined by the presence of liver fat accumulation exceeding 5% of hepatocytes in the absence of significant alcohol intake (20 g per day for men and 10 g per day for women), viral infection, or any other specific aetiology of liver disease. NAFLD encompasses a histological spectrum ranging from simple steatosis (SS) to non-alcoholic steatohepatitis (NASH), which is characterized by SS plus necroinflammation. NASH can have different stages of fibrosis ranging from absent (stage F0) to cirrhosis (stage F4). SS, NASH, and different fibrosis stages can only be differentiated by liver biopsy [118].

More than 50% of adults in the EU 27 countries are considered to be overweight or obese. According to the OECD, 34.6% of the adult population in the EU 27 is overweight and 15.5% is obese (Fig. 16, page 34). Obesity presents greater health risks than being overweight. The prevalence of obesity varies threefold among EU 27 countries, from less than 10% in Romania, Switzerland and Italy to over 20% in the United Kingdom, Ireland, Malta and Iceland. Overweight and obesity rates are much lower than average in France, Italy and Switzerland but are increasing in these countries. In this context, NAFLD is highly endemic in Europe where it represents a major potential threat to public health.

Our search retrieved 11 European studies that estimated NAFLD prevalence (Table 9, page 35). Four were population-based studies: the Study of Health in Pomerania (SHIP) [119]; a study in the province of Barcelona [120]; the DIONYSOS study in Italy [121]; and the RISC study (a large study by the European Group for the Study of Insulin Resistance on the relationship between insulin sensitivity and cardiovascular disease) [122]. NAFLD was diagnosed by ultrasonography except in the RISC study where the fatty liver index was calculated using an algorithm based on body mass index (BMI), waist circumference, triglycerides (TG's), and gamma-glutamyl transpeptidase (GGT), giving an accuracy of 0.84 (95% CI 0.81-0.87) in detecting fatty liver [122].

In the Barcelona and DIONYSOS studies, NAFLD prevalence was 26%, in the SHIP study it was 30.4% and in the RISC study 33% of patients had a high probability of having the disease [119-121].

A recent Romanian study using ultrasonography estimated NAFLD prevalence to be 20% in a large sample of patients hospitalized for internal and gastrointestinal diseases [123]. A study in Greece revealed evidence of NAFLD in 31% and of NASH in 40% of autopsied cases of ischaemic heart disease or traffic accident death (after exclusion of hepatitis B seropositivity or known liver disease) [124]. One German [125] and two Italian [126, 127] studies have investigated NAFLD prevalence in children. A high prevalence (36-44%) of NAFLD was found in obese children, regardless of the manner used to diagnose the disease. NAFLD is known to be highly correlated with diabetes. Two major European studies [128, 129] reported NAFLD prevalence rates of 42.6-69.5% in large samples of type 2 diabetic patients.

34.6%

Of the adult population in the EU27 is overweight according to the OECD.

26%

higher over-all health costs at 5 year follow up for individuals with sonographic fatty liver disease and increased serum ALT.

The presence of NAFLD carries an increased risk of overall mortality and of mortality related to cardiovascular disease (CVD) and liver disease. A cohort of 1,804 patients with hospital-diagnosed NAFLD from the Danish National Registry of Patients were followed during 16 years [130]. After adjustment for sex, diabetes and cirrhosis at the baseline, NAFLD-associated age-adjusted standardized mortality ratios (SMR) were 2.3 (95% CI 2.1-2.6) for all causes, 19.7 (95% CI 15.3-25.0) for hepatobiliary disease, and 2.1 (95% CI 1.8-2.5) for CVD [130]. In the SHIP study [119], 4,160 subjects were followed during 7 years. The odd ratios for all-cause mortality and CV mortality of ultrasonographic steatosis and highest GGT quintile in men were 1.98 (95% CI 1.21-3.27) and 2.41 (95% CI 1.05-5.55), respectively. The risk was not increased in women. The analyses were adjusted for age, waist circumference, alcohol consumption, physical activity, educational level, civil status, equalized income and functional co-morbidity index. A cohort of Swedish subjects with NAFLD that had been identified by elevated liver enzymes and liver biopsy between 1980 and 1984, were assessed for mortality in comparison with the general Swedish population during a 28 year follow-up period [131].

The age, sex, and calendar-period adjusted mortality ratio was 1.69 (95% CI 1.24-2.25) for NAFLD compared to the general population, even after excluding cirrhotic patients at the baseline. CVD, malignancy and liver disease were the top three causes of death. In the Cremona study on incidence and duration of diabetes in Italy, >2,000 middle-aged individuals were followed for 15 years. The fatty liver index was significantly associated with a higher liver-related mortality in a multi-adjusted analysis [132].

NAFLD already represents an important burden for European countries. A German study investigated the SHIP cohort for the relationship between fatty liver disease, self-reported health-care utilization and costs. The average annual overall health-care costs were significantly higher at baseline and at follow-up measurements for individuals with evidence of NAFLD [133]. For example, controlling for comorbid conditions, subjects with sonographic fatty liver disease and increased serum alanine amino transferase (ALT) levels had 26% higher overall health-care costs at 5-year follow-up.

Fig. 16 *– Obesity rates among populations of European countries; OECD Health data 2008.*

Country	Author	Study year(s) and population	Case identification	Prevalence (of NAFLD unless otherwise stated)
14 EU countries	Gastaldelli [122]	2002-2004; 1400 apparently healthy subjects between 30 and 60 yr, 44% male	Fatty Liver Index*	33%
Germany	Imhof [125]	2002; 378 children and adolescents aged 12–20 yr, 49% male	Ultrasonography and liver enzymes	2% overall, 36% in obese male children
Germany	Haring [119]	2007; 4160 subjects aged 20-79 yr	Ultrasonography	30.4%
Greece	Zois [124]	2006-2008; post-mortem material from 498 patients aged 3-94 yr, 68% male	Histology	31%, NAFLD and 40% NASH
Italy	Bedogni [121]	2001-2002; 659 subjects aged 18 to 75 yr, 58% male	Ultrasonography	26%
Italy	Caserta [126]	2007-2008; 676 adolescents aged 11–13 yr, 49.5% male	Ultrasonography	12.5% (95% CI 10.0-15.3)
Italy	Sartorio [127]	2006; 268 obese children aged 6-20 yr, 44% male	Ultrasonography	44%
Italy	Targher [128]	2005-2006; 2,839 type 2 diabetic outpatients aged 40-86 yr, 55% male	Ultrasonography	69.5% (95% CI 68.5-70.5)
Romania	Radu [123]	2006-2007; 3,005 inpatients, mean age 54 yr, 44% male	Ultrasonography	20%
Spain	Caballeria [134]	2007-2008; 773 individuals aged 15-85 yr, 42% male	Ultrasonography	25.8% overall, 33.4% in men and 20.3% in women
UK	Williamson [129]	2006-2007; 939 type 2 diabetic patients aged 60-74 yr, 52% male	Ultrasonography	42.6%

* Fatty Liver Index is based on BMI, waist circumference, triglycerides, and gamma-glutamyl-transferase GGT.

Table 9 *– European studies assessing the prevalence of NAFLD.*

DRUG INDUCED LIVER INJURIES (DILI)

Drug-induced liver injury (DILI) is a major problem for affected patients and health care providers. It is also a strong consideration in differential diagnosis when abnormal liver-related chemistries are identified in persons with minimal or no symptoms. There is presently no specific diagnostic test for DILI, or a means of confidently singling out an implicated drug among potentially many. Consequently, it is an important challenge for physicians, health authorities and pharmaceutical companies [135]. The overall frequency of hepatotoxicity for all drugs has not decreased in the last 15 years despite improvements in toxicological studies and in the safety analyses of clinical trials. Furthermore, the early detection of drug hepatotoxicity remains very difficult [135]. These difficulties are partly related to the discrepancy between preclinical studies in animal species which exhibit limited negative predictive values and a number of cases of liver injury in humans, whereas no signal has been detected in animal models.

The difficulty of liver injury detection is also related to the diversity of liver injury expression. Indeed, all liver cells can be affected by drugs [135]. The types of lesions may also vary in their clinico-pathological manifestations, according to the mechanism of hepatotoxicity, the drug itself, details of the treatment course (dosage, duration of treatment), and the susceptibility of the person taking the agent. It is noteworthy that besides the large number of “classical” drugs (more than 1,200) reported to exhibit potential hepatotoxicity [136], other agents should also be taken into consideration. These include the excipients [137] present in drug formulations, herbal medicines which are increasingly consumed and often not disclosed [138-140], and recreational and illegal compounds [141, 142]. These general aspects are particularly well illustrated by psychotropic agents. A large proportion of drug hepatotoxicity occurs as an idiosyncratic event (DILI), so that its prevalence and incidence is still only partially known despite recent improvements [135, 143]. A notable exception is accidental or suicidal paracetamol intoxication, which shows a dose-related liver toxicity, particularly when in combination with alcohol. The majority of data are provided by retrospective studies of databases from pharmacovigilance centres and/or pharmaceutical companies. What we currently know about the burden of DILI may only represent the ‘tip of the iceberg’ [135].

Few epidemiological data on DILI in Europe are available. In an analysis of a Swedish database of 1,664 cases seen for the first time between 1995-2005 DILI with at least a possible causal relationship was found in 77 cases (6.6%). 38 cases (3.3%) were referred for evaluation to the out-patient clinic whereas 3% had a follow-up after hospitalization for DILI [144].

In the UK the incidence of DILI in the general population has been estimated to be 2.4 cases per 100,000 person years (based on the UK-based General Practice Research Database) [145].

A recent prospective study performed over three years in France in an area comprising 81,000 inhabitants showed an incidence of 14 cases per 100,000 persons and corresponded to a number of events 16 times higher than that collected by pharmacovigilance centres [146].

Retrospective studies suggest that drugs may have caused around 10-20% of all cases of fulminant and subfulminant hepatitis [147, 148]. In a French study 5.5% of liver transplantations were related to drug-induced acute liver failure, of which 36.4% were due to paracetamol (acetaminophen) intake [149]. Of the 674 DILI references new to the HEPATOX database between September 2010 and August 2011, 16% concerned neuropsychiatric compounds, including carbamazepine, phenytoin and valproic acid. These data are consistent with data collected in the VigibaseTM [150].

HAEMOCHROMATOSIS

Hereditary haemochromatosis is a disease of iron regulation that results in excessive iron absorption, and ultimately, in iron overload. It is associated with an increased incidence of hepatic cirrhosis, diabetes mellitus, cardiomyopathy, and other clinical complications. It is one of the few genetic diseases for which a simple and effective therapy exists; the removal of iron by phlebotomy improves survival in symptomatic persons [151, 152]. When phlebotomy is begun prior to the development of cirrhosis or diabetes, affected people appear to have a normal life expectancy [153]. Symptoms of haemochromatosis are nonspecific, have a gradual onset and mimic other common disorders. As a result, they may be attributed to other causes, and diagnosis is often delayed.

29 fold

The increase in female in-patient admission rates attributable to haemochromatosis between 1989/1990 and 2002/2003 in the UK.

Temporal trends in the diagnosis of haemochromatosis have been studied using inpatient and day-case admissions in England and mortality statistics in England and Wales. In England during 1989/1990 to 2002/2003, there was an increase in both genders in age-standardized in-patient admission rates attributable to haemochromatosis (Figure 17, page 38). In men, the admission rate rose by 269%, from 0.64 to 2.36 per 100,000. In women, the admission rates were lower, but the absolute increase was similar at 290% (0.21 to 0.81 per 100,000) (Fig. 17a).

Day-case admissions rose even more markedly during the time period studied, the age-standardized admission rate for men rising 11-fold from 2.78 to 34.9 per 100,000, and for women rising 19-fold from 0.58 to 11.67 per 100,000 (Fig. 17b) [154].

Haemochromatosis is a result of mutations in the HFE gene which encodes for the human haemochromatosis protein. These mutations can be used to assess prevalence. In two population-based studies conducted in northern Norway, a total of 6,297 women and 5,012 men were analysed for serum ferritin (s-ferritin) and transferrin saturation. Those with levels above the reference limits in two separate blood samples (74 women and 94 men in Sør-Varanger and 253 women and 285 men in Tromsø) were tested for three different HFE mutations: C282Y, H63D and S65. In Sør-Varanger, the prevalence of the C282Y/C282Y mutation among men and women was 0.22% in both genders. In the Tromsø survey, the prevalence among men and women was 0.12% and 0.05%, respectively [155]. The allelic frequencies of C282Y and H63D have also been estimated in a sample of 200 individuals evenly-distributed over North-Eastern Romania. They were either healthy blood-donors or were persons who presented as ambulatory or hospital patients with various diagnoses, excluding hepatic diseases, heart diseases or diabetes. The calculated allelic frequency of the two mutant alleles in this population sample was 1.75% (95% CI 0.7-3.7) for C282Y and 13.25% (95% CI 10.4-16.5) for H63D [156].

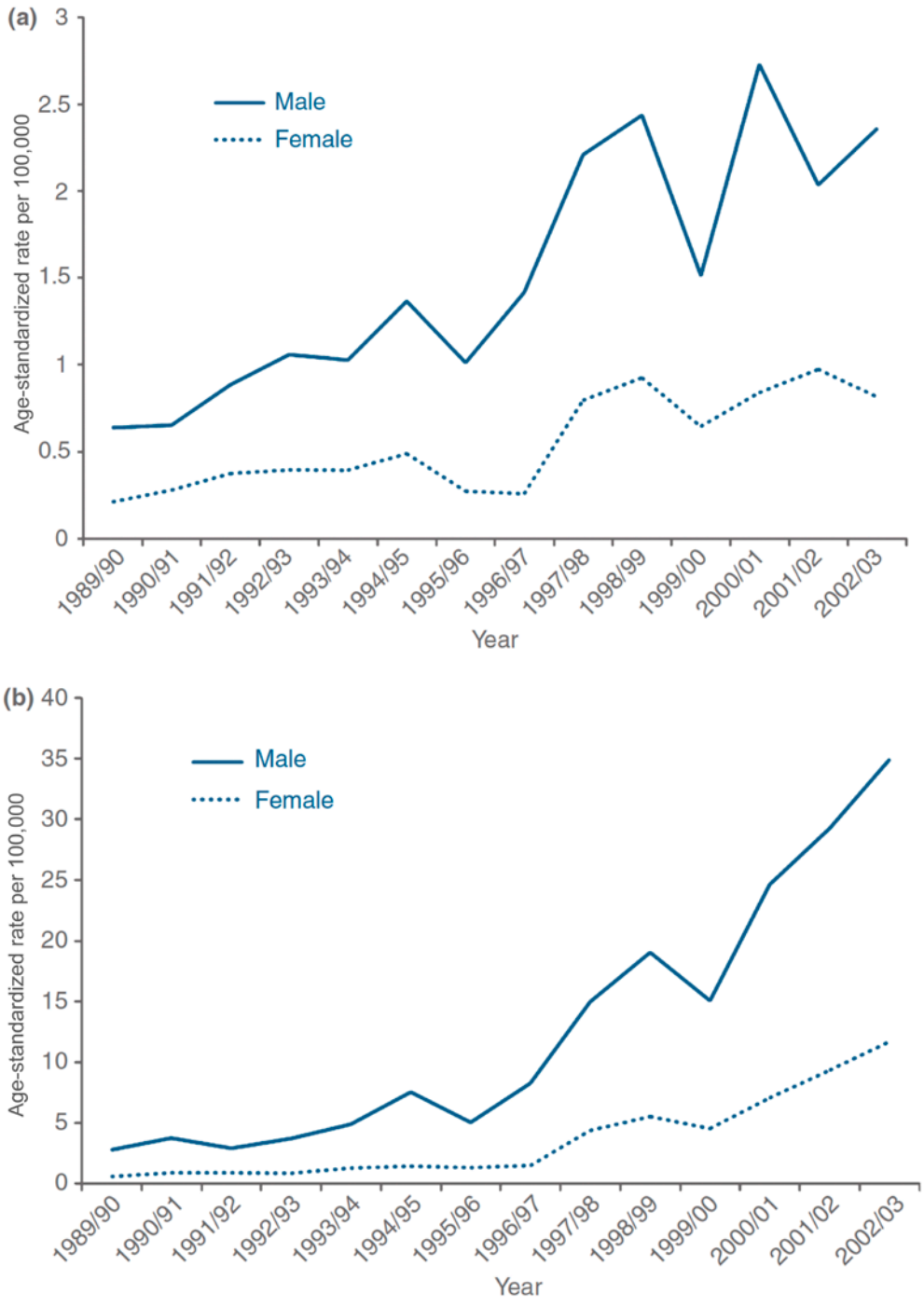

Fig. 17 *– Hospital admissions attributed to haemochromatosis in England from 1989/1990 to 2002/2003.*
(a) Age-standardized in-patient admission rate per 100,000 per year.
(b) Age-standardized day-case admission rate per 100,000 per year [154].

A registry of patients with genetic haemochromatosis was established in the south of France, together with a regional health network to ensure the inclusion of all diagnosed patients. Patients were included in the registry over a 6-year period from 2002 to 2008 if they were homozygous for the C282Y mutation and were classified in stages 2-4 of the French National Authority for Health haemochromatosis classification (2 = biological iron overload, 3 and 4 = increasingly severe clinical manifestations of iron overload). In total, 352 symptomatic C282Y homozygotes were identified, giving a total prevalence of 1.83 per 10,000 (95% CI 1.63-2.02) in subjects over 20 years old and 2.40 per 10,000 (95% CI 2.15-2.65) among subjects of European descent. Among Europeans, the total calculated penetrances were 15.8% for those in stage 2 or higher, 12.1% for those in stage 3 or 4, and 2.9% for those in stage 4 [157].

A Danish epidemiological population survey assessed the penetrance of the most frequent HFE gene variants in ethnic Danish men. A cohort of 6,020 men aged 30-53 years was screened for C282Y, H63D and S65C variants by restriction fragment length polymorphism analysis (RFLP). Subsequently, iron-status markers (serum transferrin saturation and serum ferritin) were analysed in 1,452 men. The C282Y allele was present in 5.6%, H63D in 12.8%, and S65C in 1.8% of the men. Among untreated C282Y homozygotes with available iron-status markers (n = 21), 89% had elevated transferrin saturation, 94% had elevated ferritin, and 88% had elevation of both iron-status markers; seven out of 16 (44%) had ferritin values >800 µg/l [158].

1.83%

The prevalence of C282Y homozygotes per 10,000 of a Southern French population.

AUTOIMMUNE HEPATITIS

There is no single specific test for diagnosis of autoimmune hepatitis (AIH). However, sero-immunological and molecular biological tests contribute to discrimination of AIH from other aetiologies of chronic hepatitis, in particular from chronic viral infection, the most common cause of chronic hepatitis. Diagnosis relies on a combination of indicative features of AIH and on the exclusion of other causes of chronic liver diseases. The clinical appearance ranges from an absence of symptoms, to a severe or fulminant presentation and it responds to immunosuppressive treatment in most cases. An association with extrahepatic autoimmune diseases is frequent.

Unfortunately, very little data is available on the incidence and prevalence of AIH. Much of the information regarding AIH comes from studies of idiopathic chronic active hepatitis. Prior to the introduction of the 'Autoimmune Hepatitis: Revised Scoring System' in 1999, there was no standardized way of evaluating patients with suspected AIH and, as a result, the studies included somewhat heterogeneous patient populations. Nevertheless, based on limited epidemiological data, the prevalence of AIH is estimated to range from 5-20 cases per 100,000 among the Caucasian population in Western Europe. It is estimated to account for up to about 20% of cases of chronic hepatitis among the Caucasian population of North America and Western Europe [159].

Three recent population-based studies in European populations have estimated incidence and prevalence of AIH (Table 10, below). In a Norwegian population, a mean annual incidence of 1.9 cases of AIH per 100,000 person-years and a prevalence of 16.9 per 100,000 of the population were observed [160]. A Spanish study drew on all patients who were newly-diagnosed with AIH in 2003 in the Gastroenterology departments of eight acute-care reference hospitals in the province of Valencia, covering ~1.8 million inhabitants over 14 years of age. The AIH incidence rate was 1.07 per 100,000 inhabitants overall, with 1.96 and 0.12 cases per 100,000 for females and males, respectively [161]. In a Swedish study, the incidence of AIH was 0.85 per 100,000 inhabitants (95% CI 0.69-1.01), its prevalence was 10.7 per 100,000 (95% CI 8.8-13.1), 76% of cases were female and 30% of patients with AIH had liver cirrhosis [162].

A German study has shown that AIH is commonly associated with liver cirrhosis but not with HCC. 32% of a cohort of 278 patients with AIH were diagnosed with liver cirrhosis. The average follow-up was 4.8 years per patient and, during this period, none of the patients developed HCC. This study should be interpreted with caution because of its lack of power but the incidence of HCC associated with AIH-induced cirrhosis appears to be significantly lower than that associated with other causes of liver cirrhosis, such as chronic viral hepatitis, alcohol or haemochromatosis [163].

Country	Author	Study year(s) and population	Incidence per 100,000 person-years	Prevalence per 100,000 inhabitants
Norway	Boberg [160]	1986-1995; Aker University Hospital registry	1.9	16.9
Spain	Primo [161]	2003; Valencia hospitals' registries	1.07	
Sweden	Werner [162]	The Swedish Internal Medicine Liver Club registry	0.85	10.7

Table 10 *– European studies assessing the prevalence and incidence of autoimmune hepatitis.*

PRIMARY **BILIARY CIRRHOSIS (PBC)**

PBC is an autoimmune liver disease characterised by the presence in serum of highly-specific anti-mitochondrial antibodies (AMAs) and progressive destruction of intrahepatic bile ducts, resulting in chronic cholestasis, portal inflammation and fibrosis that can lead to cirrhosis and, ultimately, to liver failure. The disease predominantly affects women, who are diagnosed typically in their fifth and sixth decade, although younger patients have been described, including children (albeit rarely).

Data on the incidence and prevalence of PBC have generally been obtained passively and so might not indicate true rates in the general population. Indeed, a population-based approach to the detection of cases has little feasibility for PBC because of its rarity. Regional differences in incidence and prevalence of PBC are probably secondary to variability in factors such as diagnostic criteria, case-finding methods, doctors' awareness, and quality of health-care systems.

On the basis of case-finding studies, the disease has been found to be most frequent in northern Europe and North America. The highest prevalence and incidence rates have been reported in Scandinavia, Great Britain and the northern Midwest region of the USA. An exception to this pattern is the high rate found in the Spanish area of Sabadell [164]. Some researchers suggest that the incidence of PBC is growing. In the UK, incidence rates rose from 0.58 to 2.05 cases per 100,000 population per year in Sheffield from 1980-1999 [165] and from 1.1 to 3.2 cases per 100,000 population per year in Newcastle-upon-Tyne from 1976-1994 [166, 167]. This increase was paralleled by rise of prevalence to more than 20 cases per 100,000 in the mid-to-late 1990's. In Finland, the age-standardized prevalence of PBC increased between 1988 and 1999 from 10.3 (95% CI 97-110) to 18.0 (95% CI 172-189) per 100,000 inhabitants.

Over the same period, incidence increased from 12 (95% CI 10-14) to 17 (95% CI 15-20) per million inhabitants per year. The annual average increases in prevalence and incidence were 5.1% (95% CI 4.2-5.9%, $p<0.0001$) and 3.5% (95% CI 0.9%-6.0%, $p=0.008$), respectively [168]. It remains to be established whether these changes are due to rising disease incidence or reflect improved detection of mild asymptomatic cases or of slowly progressing disease.

The progression of PBC in patients is extremely variable. Studies of asymptomatic patients suggest that their survival is reduced when compared with an age- and gender-matched population. In a Canadian study, authors retrospectively reviewed all patients with abnormal liver biochemical tests, positive AMA tests and liver-biopsy-compatible PBC. Among the 91 patients concerned, the standardized mortality ratio was 2.87 (95% CI 1.38-4.63) [169]. Patients may, on occasion, present de novo with a variceal haemorrhage. This may be caused by non-cirrhotic portal hypertension [170] or may be secondary to cirrhosis. Complications of variceal haemorrhage are not predicted by standard prognostic indices. Once PBC has progressed to frank cirrhosis, liver complications do not differ much from those seen in cases of cirrhosis associated with other causes. Complications of portal hypertension (i.e. ascites and hepatic encephalopathy) are typical in end-stage PBC. The occurrence of hepatocellular carcinoma in individuals with PBC is similar to that associated with other forms of cirrhosis and warrants surveillance in patients at advanced stages of disease [171].

PRIMARY **SCLEROSING CHOLANGITIS (PSC)**

PSC is a chronic cholestatic liver disease of an unknown aetiology that is characterized by chronic inflammation, destruction and fibrosis of the intrahepatic and/or extrahepatic biliary tree. This aberrant inflammatory response may ultimately lead to cirrhosis, end-stage liver disease, and the need for liver transplantation [172].

Three recent European studies have investigated PSC incidence. In a large population-based study in Sweden an incidence of 1.22 (95% CI 1.06-1.40) per 100,000 person-years was observed between 1992 and 2005 [173]. In a British population-based study of more than five million person-years between 1984 and 2003, PSC incidence was 0.91 (95% CI 0.68-1.21) per 100,000 person-years [174]. In a second UK study based on the General Practice Research Database and conducted between 1991 and 2001, the incidence of PSC was 0.41 (95% CI 0.34-0.48) [175]. In this study, the risk of death or liver transplantation was more than tripled for PSC patients and the risk of all malignancy was more than doubled. However this last study should be interpreted with caution because the GPRD is not population-based and the code for PSC was not validated.

It should also be noted that PSC is one of the principal aetiologies of liver transplantation in cases of cholestatic disease (Fig. 18, below).

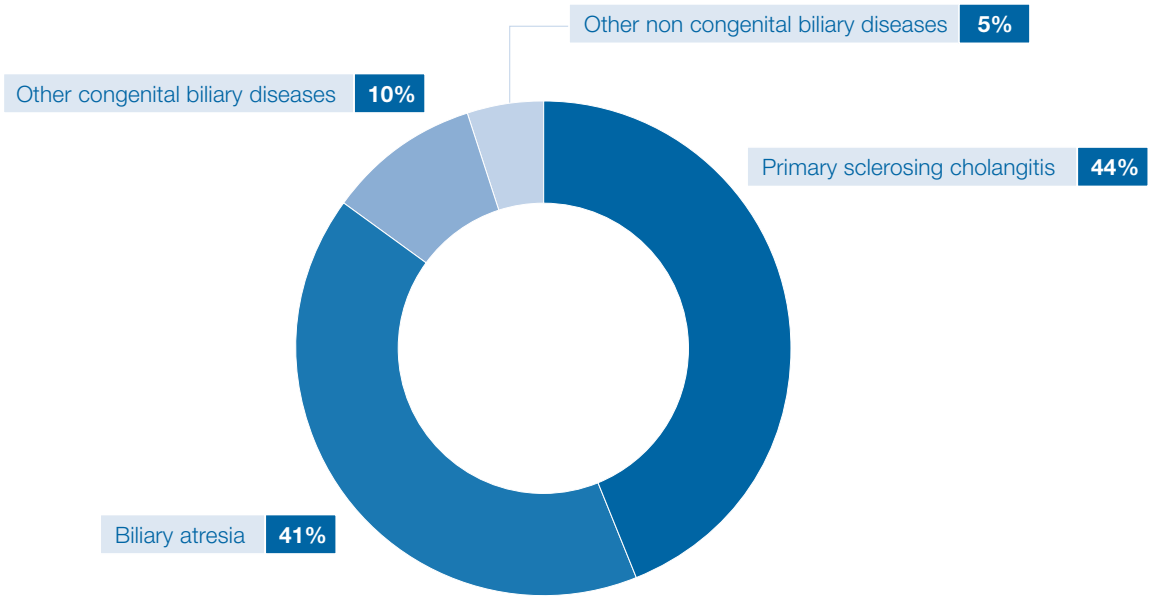

***Fig. 18** – Primary indications for liver transplantation in Europe among patients with cholestatic diseases, January 1988 to December 2009.*

CONCLUSION

Table 11 on page 44 and Table 12 on page 45 summarise the currently-available data on the incidence and prevalence of the main liver diseases in Europe. Country comparisons should be carried out with caution as these data are based on numerous different sources, sometimes with different epidemiological definitions. However, it is clear that data in the literature is scarce and that more efforts should be made to fully understand the extent of the burden of liver disease in Europe.

Table 13 on page 46 and Table 14 on page 47 compare the epidemiological data for some of the liver diseases reviewed here with data available for other diseases. Table 13 shows the mortality caused by primary liver cancer and by cirrhosis in comparison with that caused by colon cancer, breast cancer, chronic obstructive respiratory diseases and nephritis diseases. All data are derived from the WHO database to enhance comparability. Table 13 clearly demonstrates that both primary liver cancer and cirrhosis cause a non-negligible number of deaths compared to other diseases. Finally, Table 14 compares available prevalence data for HBV and HCV with the prevalence of HIV in adults, showing that fewer people in Europe are living with HIV than are living with HBV or HCV.

	Cirrhosis	Primary liver cancer	Hepatitis B
Austria	-	2.7 – 7.9	7
Belgium	-	1.4 – 3.8	5.3
Bulgaria	-	2.2 – 5.6	-
Czech Republic	-	2.5 – 6.4	3.5
Cyprus	-	-	0.8
Denmark	11.2 – 26.5	1.9 – 6.3	0.5
Estonia	-	1.5 – 3.5	5.8
Finland	-	2.2 – 5.2	-
France	-	0.8 – 13.8	0.2
Germany	-	2.2 – 6.2	1.4
Greece	-	13.2 - 4.3	0.8
Hungary	-	1.8 – 6.1	1.2
Iceland	-	-	11.2
Ireland	-	1.5 – 3.4	1.8
Italy	-	4.4 – 21.1	1.8
Latvia	-	-	7.4
Lithuania	-	1.4 – 4.1	4.1
Luxembourg	-	3.8 – 9.8	1.1
Netherlands	-	0.8 – 2.4	1.7
Norway	-	-	3.2
Malta	-	-	3
Poland	-	1.7 – 3.2	1.2 - 4.4
Portugal	-	1.2 – 3.5	0.8
Romania	-	-	8.5
Slovakia	-	2.3 – 5.8	2.3
Slovenia	-	2.3 – 7.7	0.9
Spain	-	9.6 – 2.5	1.5
Sweden	12.9 – 17.7	1.8 – 3.3	2.4
UK	14.55 - 26	1.9 – 4.2	0.7

† For sources see related sections of the report
HCV incidence data are available from the ECDC, but this is subject to caution and it is not included here
This table summarises the data available from the previous sections and, given the range when multiple sources are available, it cannot be used for comparison.

Table 11 *– Incidence of liver diseases per 100,000 inhabitants per year in Europe (where data is available) †.*

	Cirrhosis	Hepatitis B	Hepatitis C	NAFLD
Austria	-	-	-	-
Belgium	-	0.66 – 0.7	0.12	-
Bulgaria	-	-	-	-
Czech Republic	-	0.3	-	-
Cyprus	-	-	-	-
Denmark	0.07 – 0.13	-	-	-
Estonia	-	-	-	-
Finland	-	0.2	-	-
France	0.2 -0.5	0.65	0.65 – 0.71	-
Germany	-	-	-	2
Greece	-	0.6 – 3.4	-	31 – 40
Hungary	-	-	-	-
Iceland	-	-	-	-
Ireland	-	0.1	-	-
Italy	-	0.6 – 1.0	2.6	10 – 26
Latvia	-	-	-	-
Lithuania	-	-	-	-
Luxembourg	-	0.6	-	-
Netherlands	-	0.1 – 0.4	0.6	-
Norway	-	-	-	-
Malta	-	-	-	-
Poland	-	-	-	-
Portugal	-	-	-	-
Romania	-	5.6	3.2	20
Slovakia	-	0.6	-	-
Slovenia	-	-	-	-
Spain	-	0.4 – 1.0	-	25.8
Sweden	-	-	-	-
UK	0.076	-	-	46.2

† For sources see related sections of the report

This table summarises the data available from the previous sections and, given the range when multiple sources are available, it cannot be used for comparison.

Table 12 *– Prevalence (%) of liver diseases in Europe (where data is available) †*

	Population (millions)	Colon and rectum cancers	Breast cancer	Chronic obstructive pulmonary disease	Nephritis and nephrosis	Liver cancer	Cirrhosis of the liver
Austria	8.3	2,488	1,642	2,425	913	782	1,393
Belgium	10.6	3,237	2,449	4,635	1,294	671	1,130
Bulgaria	7.6	2,719	1,428	1,676	1,351	825	1,794
Czech Republic	10.3	4,317	1,862	2,082	1,059	792	2,043
Denmark	5.5	2,355	1,439	3,037	543	314	889
Estonia	1.3	426	246	222	109	90	373
Finland	5.3	1,120	859	1,045	285	397	1,236
France	62.0	20,552	13,950	8,325	7,227	8,024	8,014
Germany	82.3	30,992	19,711	24,130	11,789	6,895	15,683
Greece	11.1	2,568	2,196	2,089	1,964	1,605	813
Hungary	10.0	4,940	2,222	4,377	565	758	4,870
Ireland	4.4	1,039	806	1,248	392	199	287
Italy	59.6	20,269	13,222	21,527	8,744	9,753	8,165
Latvia	2.3	731	478	271	259	129	465
Lithuania	3.3	976	629	805	234	155	1,379
Luxembourg	0.5	134	82	113	36	35	73
Netherlands	16.5	5,423	3,764	6,359	1,605	647	852
Norway	4.8	1,762	710	2,033	581	170	215
Poland	38.1	12,441	6,408	8,261	4,944	2,137	8,008
Portugal	10.7	4,278	1,896	2,690	2,191	893	1,537
Romania	21.4	5,359	3,225	5,392	2,200	2,653	10,226
Slovakia	5.4	1,960	823	675	650	379	1,513
Slovenia	2.0	788	462	399	150	191	629
Spain	44.5	15,343	6,711	13,843	7,085	4,580	4,694
Sweden	9.2	2,937	1,694	2,649	794	604	650
United Kingdom	61.2	18,951	14,343	29,069	4,804	3,470	7,767
TOTAL	498.3	168,107	103,255	149,377	61,767	**47,147**	**84,697**

Table 13 *– Inter-country comparison of the number of deaths associated with selected diseases compared to liver diseases based on death certificates (age-standardized); WHO, 2008.*

	Hepatitis B †	Hepatitis C †	HIV (95% CI) *
Austria	-	-	0.3 (0.2 - 0.4)
Belgium	0.66 – 0.7	0.12	0.2 (0.2 - 0.3)
Bulgaria	-	-	0.1 (0.1 - 0.1)
Czech republic	0.3	-	-
Cyprus	-	-	<0.1 (<0.1 - <0.1)
Denmark	-	-	0.2 (0.1 - 0.2)
Estonia	-	-	1.2 (1.0 - 1.5)
Finland	0.2	-	0.1 (0.1 - 0.1)
France	0.65	0.65 – 0.71	0.4 (0.3 - 0.5)
Germany	-	-	0.1 (0.1 - 0.2)
Greece	0.6 – 3.4	-	0.1 (0.1 - 0.2)
Hungary	-	-	<0.1 (<0.1 - 0.1)
Iceland	-	-	0.3 (0.2 - 0.4)
Ireland	0.1	-	0.2 (0.2 - 0.3)
Italy	0.6 – 1.0	2.6	0.3 (0.2 - 0.3)
Latvia	-	-	0.7 (0.5 - 0.9)
Lithuania	-	-	0.1 (<0.1 - 0.1)
Luxembourg	0.6	-	0.3 (0.2 - 0.4)
Netherlands	0.1 – 0.4	0.6	0.1 (0.1 - 0.1)
Norway	-	-	0.2 (0.1 - 0.3)
Malta	-	-	0.1 (0.1 - 0.2)
Poland	-	-	0.1 (0.1 - 0.1)
Portugal	-	-	0.6 (0.4 - 0.7)
Romania	5.6	3.2	0.1 (0.1 - 0.1)
Slovakia	0.6	-	<0.1 (<0.1 - <0.1)
Slovenia	-	-	<0.1 (<0.1 - 0.1)
Spain	0.4 – 1.0	-	0.4 (0.3 - 0.4)
Sweden	-	-	0.1 (0.1 - 0.2)
UK	-	-	0.2 (0.2 - 0.3)

* Source: WHO, 2008 (prevalence is given with 95% confidence interval)

† For sources see related sections of the report. A range is given when multiple sources are available.

Table 14 *– Inter-country comparison of the prevalence of HBV, HCV and HIV.*

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